AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

Approcci interdisciplinari in reumatologia - 7ª edizione

MALATTIE REUMATICHE E DISORDINI ENDOCRINO-METABOLICI

TERAPIA BIOLOGICA E CON JAK INIBITORI NELL'AR: EFFETTI SUL METABOLISMO

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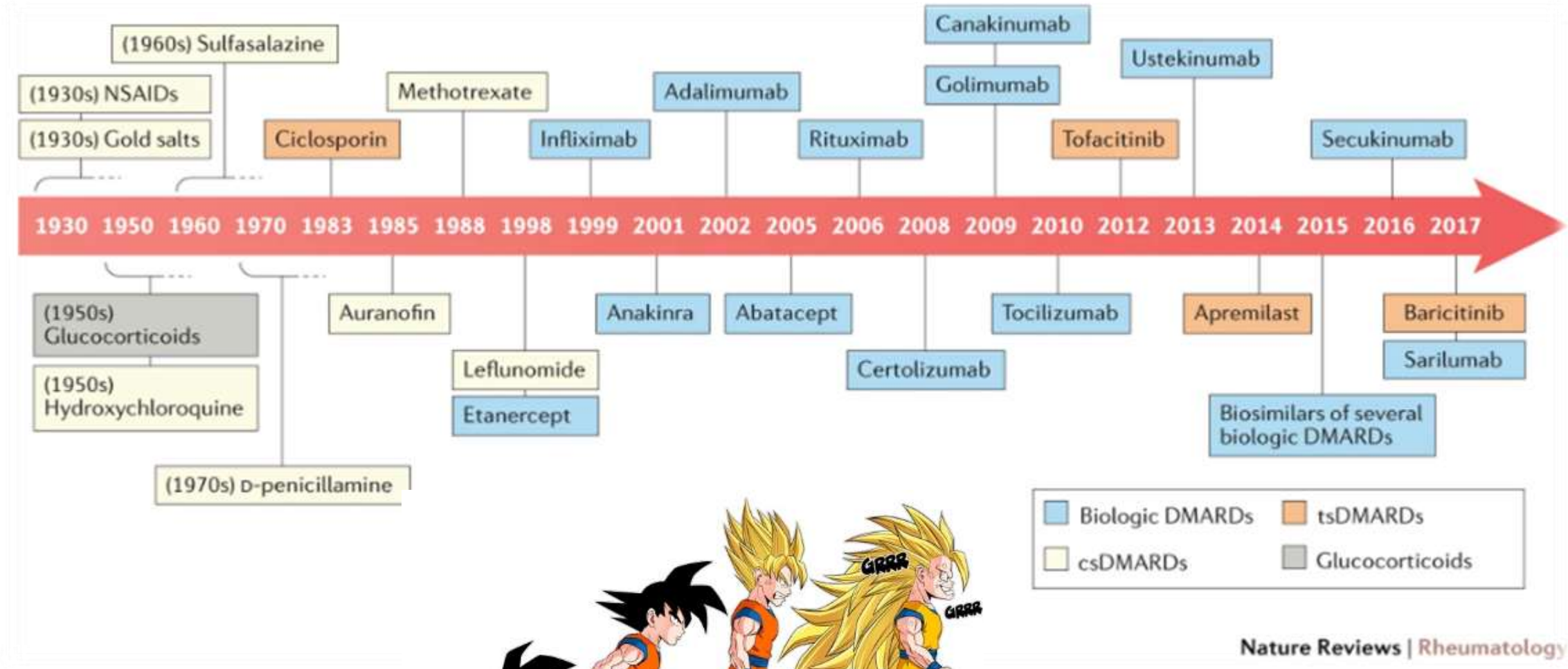
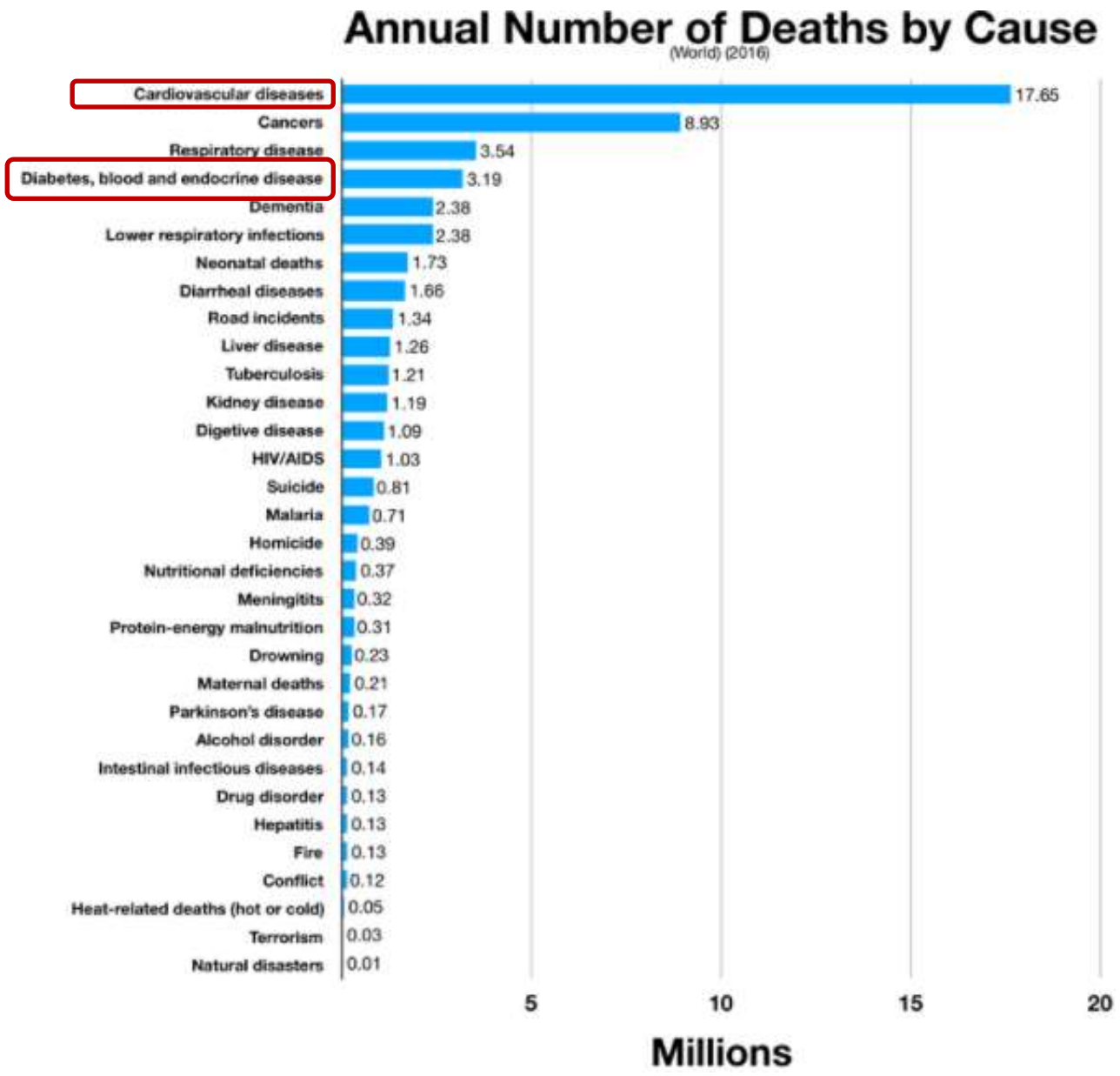
AOU Città della Salute e della Scienza di Torino,
S.C. Reumatologia

BIOLOGICS EVOLUTION



WHO 2016


Annual Number of Deaths by Cause
(World) (2016)
Cardiovascular diseases 17.65
Cancers 8.93
Respiratory disease 3.54
Diabetes, blood and endocrine disease 3.19
Dementia 2.38
Lower respiratory infections 2.38
Neonatal deaths 1.73
Diarrheal diseases 1.66
Road incidents 1.34
Liver disease 1.26
Tuberculosis 1.21
Kidney disease 1.19
Digetive disease 1.09
HIV/AIDS 1.03
Suicide 0.81
Malaria 0.71
Homicide 0.39
Nutritional deficiencies 0.37
Meningitits 0.32
Protein-energy malnutrition 0.31
Drowning 0.23
Maternal deaths 0.21
Parkinson's disease 0.17
Alcohol disorder 0.16
Intestinal infectious diseases 0.14
Drug disorder 0.13
Hepatitis 0.13
Fire 0.13
Conflict 0.12
Heat-related deaths (hot or cold) 0.05
Terrorism 0.03
Natural disasters 0.01
5
10
15
20
Millions

CAUSES OF HOSPITAL MORTALITY IN PATIENTS WITH RA AND SLE IN A UNIVERSITY HOSPITAL: 1998–2015 ANALYSIS

Table 1. Hospital admissions and deaths per year. Data are n (%).

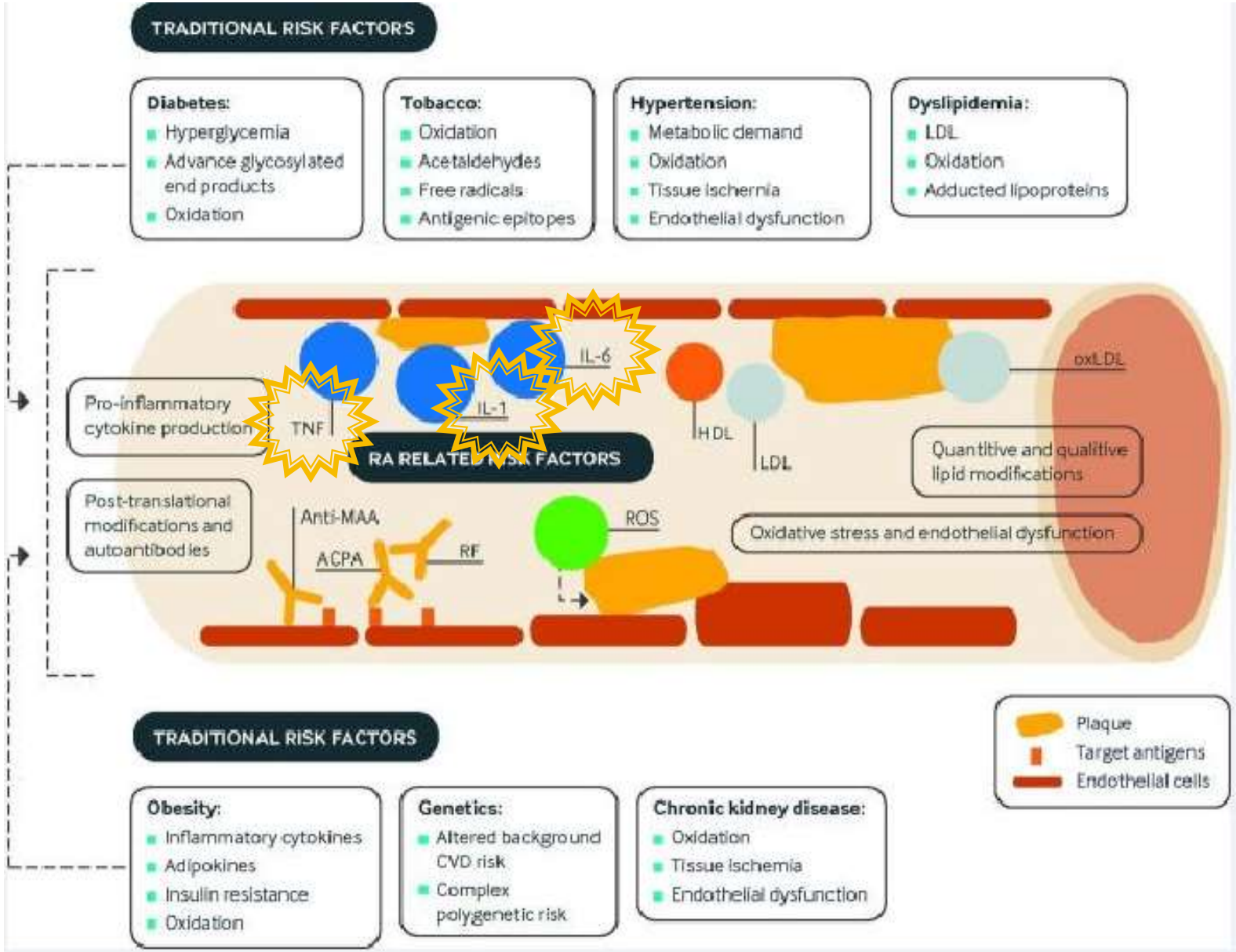
	Rheumatoid Arthritis		Systemic Lupus Erythematosus	
	Hospital Admissions, n = 467	Deaths, n = 24	Hospital Admissions, n = 863	Deaths, n = 191
1998	6 (1.3)	0 (0)	19 (2.2)	6 (31.6)
1999	12 (2.6)	3 (25)	38 (4.4)	6 (15.8)
2000	22 (4.7)	0 (0)	21 (2.4)	4 (19)
2001	14 (3)	0 (0)	36 (4.2)	5 (13.9)
2002	17 (3.6)	0 (0)	22 (2.5)	2 (9.1)
2003	26 (5.6)	0 (0)	65 (7.5)	22 (33.8)
2004	33 (7.1)	1 (3.03)	40 (4.6)	9 (22.5)
2005	28 (6)	1 (3.57)	64 (7.4)	32 (50)
2006	27 (5.8)	0 (0)	39 (4.5)	7 (17.9)
2007	34 (7.3)	0 (0)	33 (3.8)	9 (27.3)
2008	40 (8.6)	2 (5)	49 (5.6)	19 (38.8)
2009	28 (6)	0 (0)	53 (6.1)	8 (15.1)
2010	24 (5.1)	7 (29.17)	60 (7)	10 (16.7)
2011	27 (5.8)	0 (0)	51 (5.9)	9 (17.6)
2012	31 (6.6)	2 (6.45)	80 (9.3)	9 (11.3)
2013	41 (8.8)	6 (14.63)	88 (10.2)	15 (17)
2014	40 (8.6)	2 (5)	66 (7.6)	16 (24.2)
2015	17 (3.6)	0 (0)	39 (4.5)	3 (7.7)

Table 2. Mortality causes in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Data are n (%).

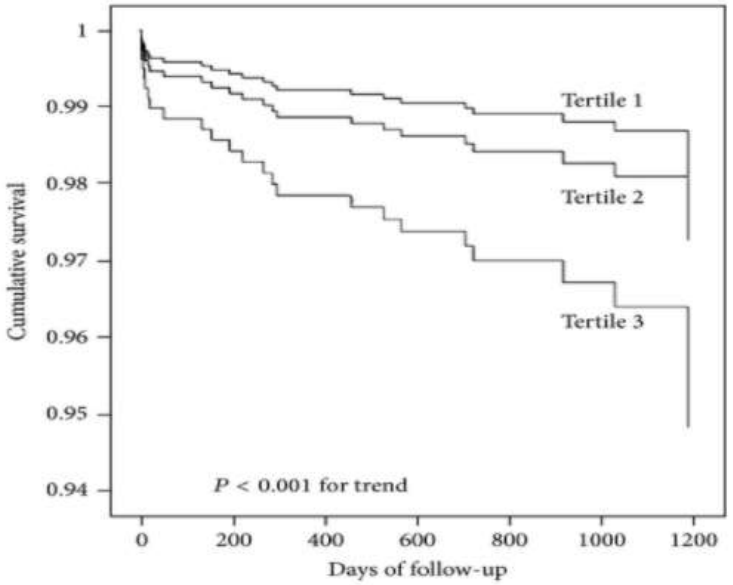
Etiology	RA, n = 24	SLE, n = 191
Acute respiratory failure	7 (29.1)	46 (24)
Sepsis, unspecified	6 (25)	39 (20.4)
Other sudden death, cause unknown	4 (16.6)	27 (14.1)
Alveolar and parietoalveolar conditions	0 (0)	12 (6.2)
Cardiac conduction disorder, unspecified	0 (0)	9 (4.7)
Systemic inflammatory response syndrome of infectious origin with organ failure	0 (0)	8 (4.1)
Cardiogenic shock	1 (4.1)	7 (3.6)
Acidosis	0 (0)	4 (2)
Pneumonia, unspecified	0 (0)	4 (2)
Hypovolemic shock	0 (0)	4 (2)
Bacterial meningitis, unspecified	0 (0)	3 (1.5)
Disorder of central nervous system, unspecified	0 (0)	3 (1.5)
Endocarditis, valve unspecified	0 (0)	3 (1.5)
Pneumonitis from food and vomit	0 (0)	3 (1.5)
Chronic kidney disease	0 (0)	3 (1.5)
Histoplasmosis, unspecified	0 (0)	2 (1)
Other lipid storage disorders	0 (0)	2 (1)
Cardiac arrhythmia, unspecified	1 (4.1)	2 (1)
Cerebrovascular diseases	2 (8.3)	2 (1)
Thoracoabdominal aortic aneurysm, without mention of rupture	0 (0)	2 (1)
Pulmonary edema	0 (0)	2 (1)
Other diseases of jaws	0 (0)	2 (1)
Dilated cardiomyopathy	0 (0)	1 (0.5)
Hypertensive encephalopathy	0 (0)	1 (0.5)
Interstitial pulmonary disease, unspecified	1 (4.1)	0 (0)
Cervical disc disorders	2 (8.3)	0 (0)

David Vega-Morales J Rheumatol. 2018

RA and CV-risk and cytokines



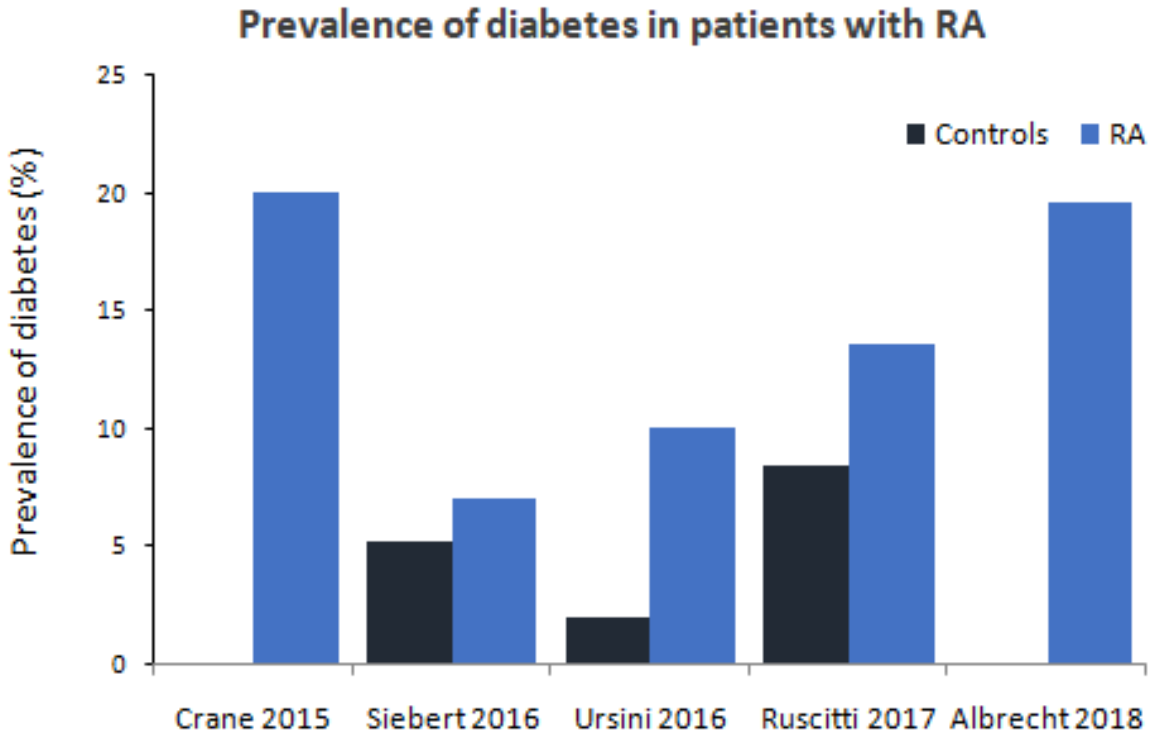
Association between serum IL-6 tertile and CVD mortality



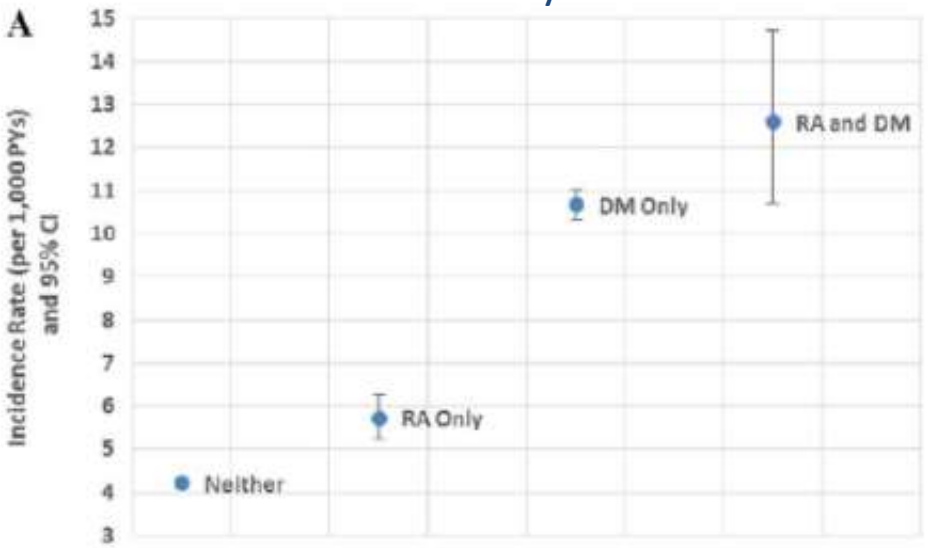
In hospitalised patients with coronary artery disease, increased serum IL-6 was statistically significantly associated with all-cause and cardiovascular mortality

Su D et alMediators Inflamm. 2013;2013:726178
England BR et al, BMJ. 2018;361:k1036. Published 2018 Apr 23.

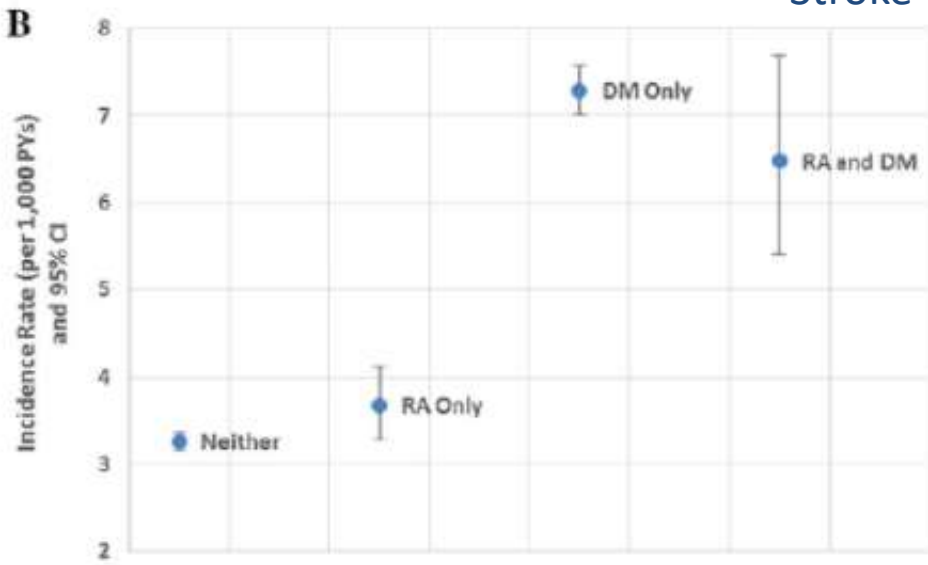
DM & RA



Myocardial infarction



Stroke

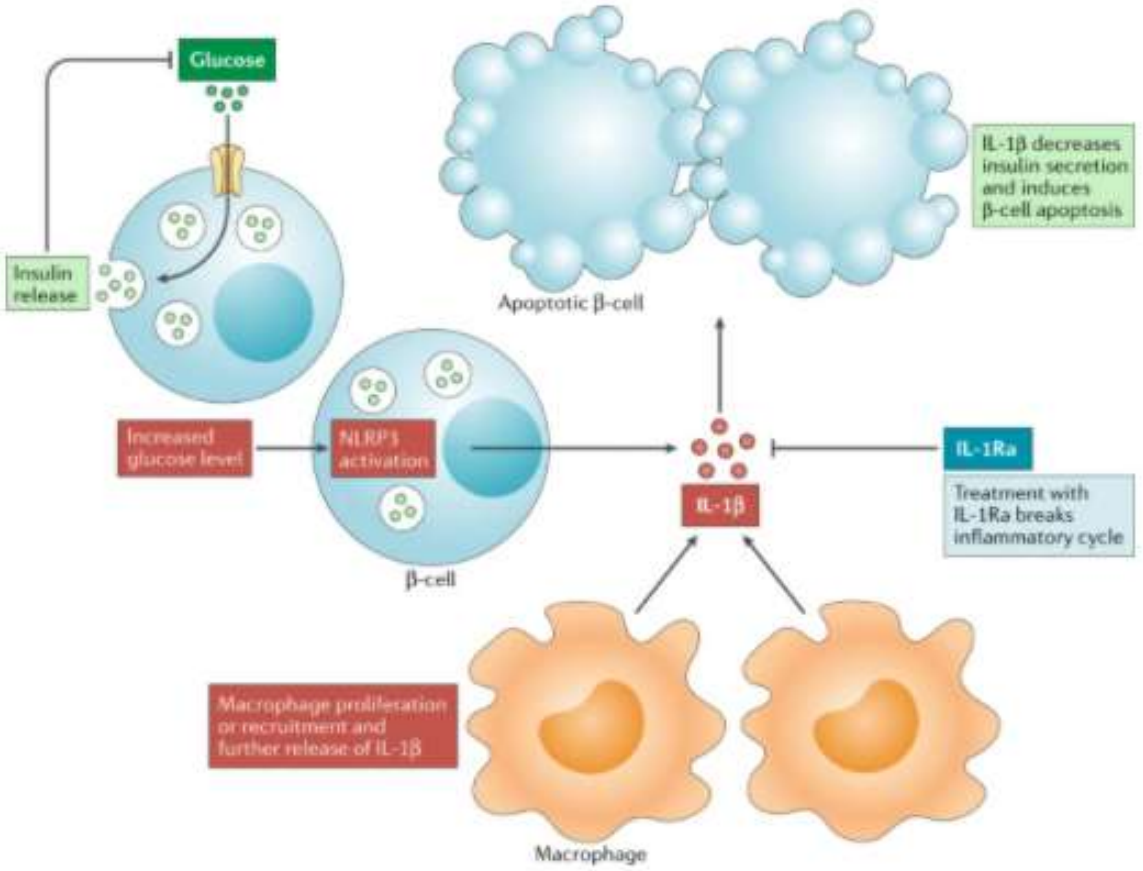


Crane MM, et al. Arthritis Care Res 2015;67:1646–55; Siebert S, et al. RMD Open 2016;2:e000267; Ursini F, et al. Medicine (Baltimore) 2016;95:e2552; Ruscitti P, et al. Medicine (Baltimore) 2017;96:e7896; Albrecht K, et al. Rheumatology (Oxford) 2018;57:329–36; Wild S, et al. Diabetes Care 2004;27:1047–53. Curtis J R et al, Arthritis Care & Research Vol. 70, No. 11, November 2018, pp 1694–1699

ROLE OF IL-1 ON METABOLISM RELATED SYNDROMES: DM1e2

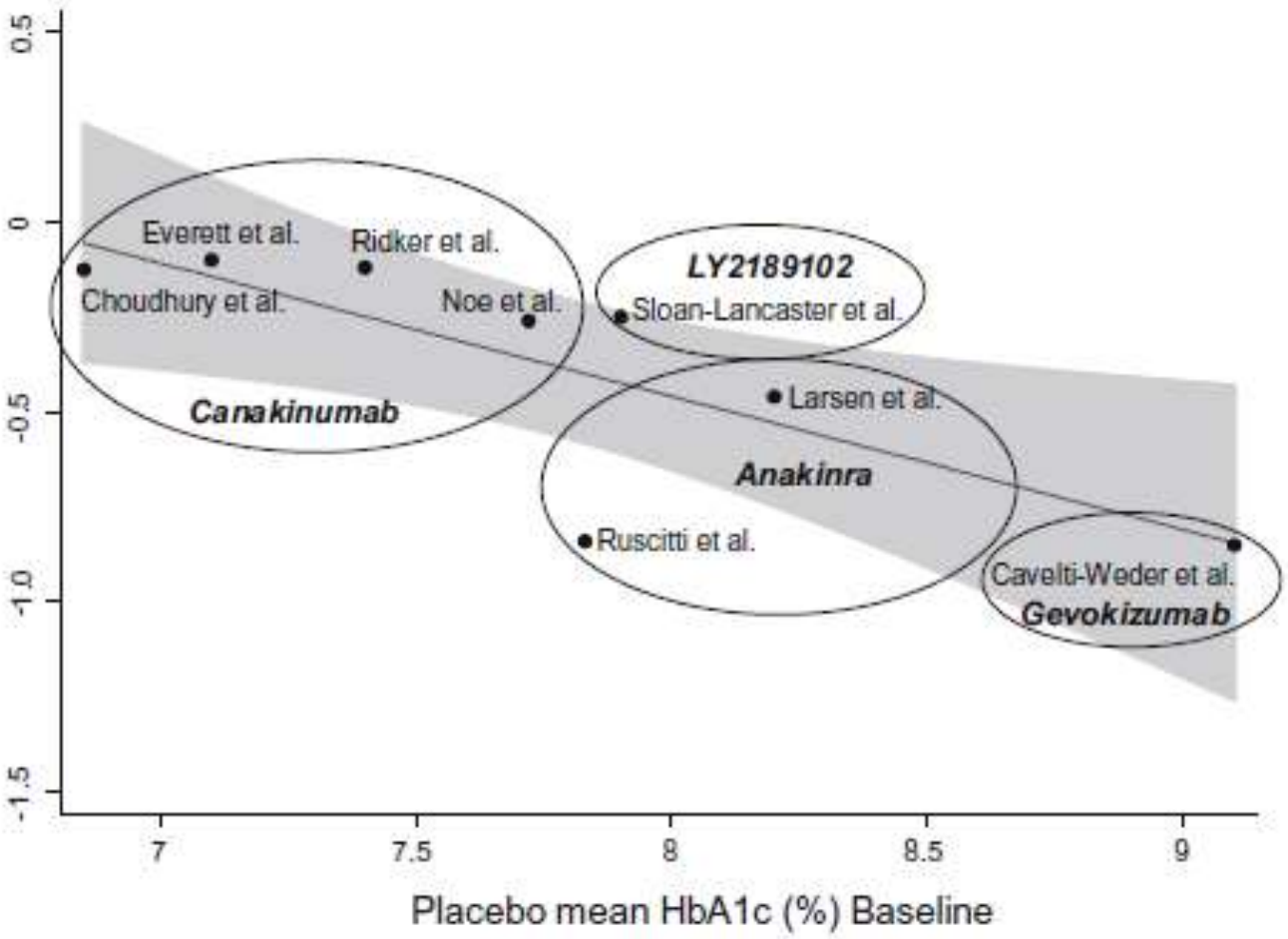
DM2 Insulino-resistenza e insufficienza delle cellule beta pancreatiche, le cui cause hanno componenti infiammatorie.

Fig. 1: Model for targeting IL-1β in islets of patients with type 2 diabetes.



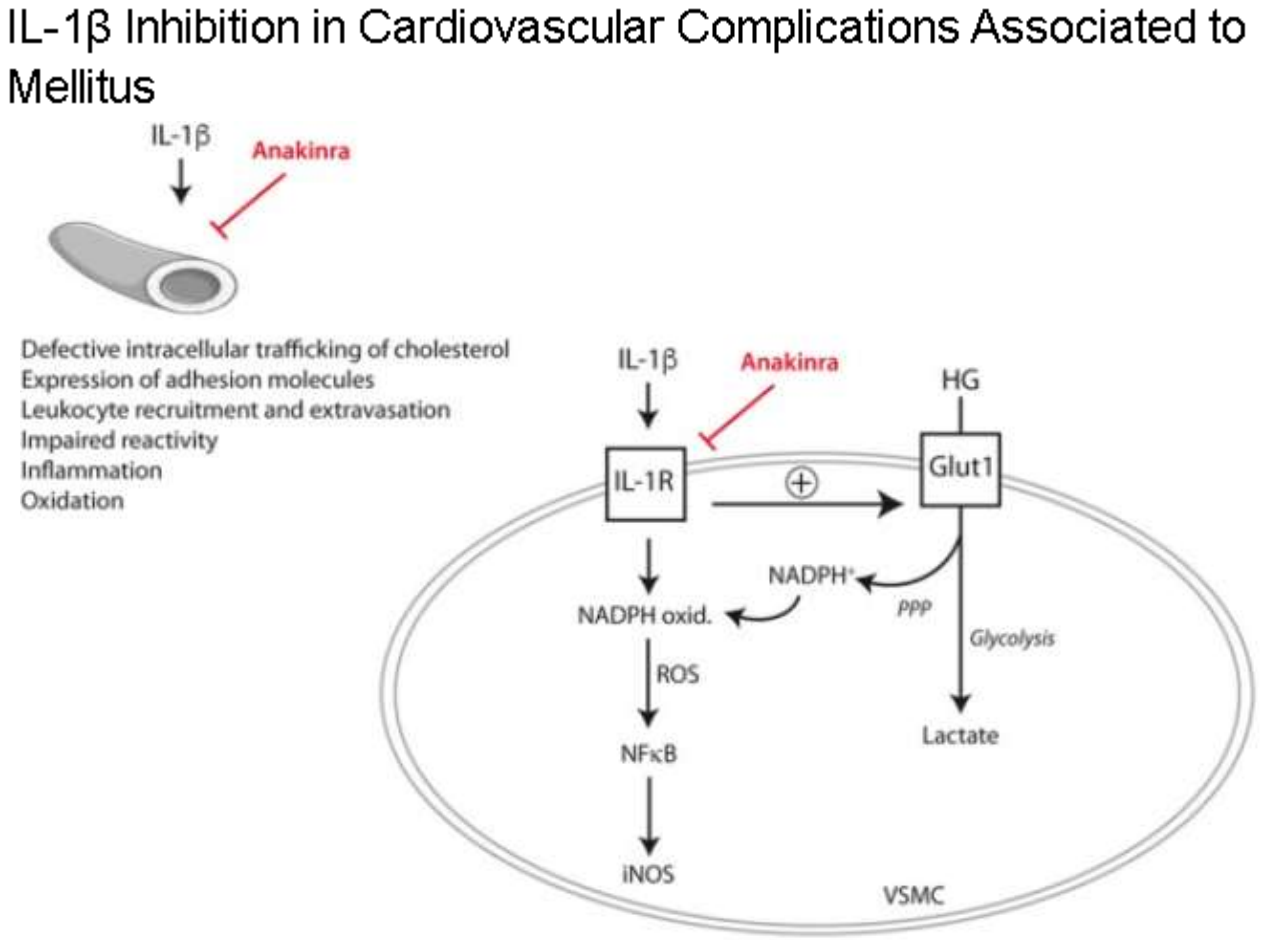
DM1 risultati contrastanti.

Treatment of type 2 diabetes by targeting interleukin-1: a meta-analysis of 2921 patients

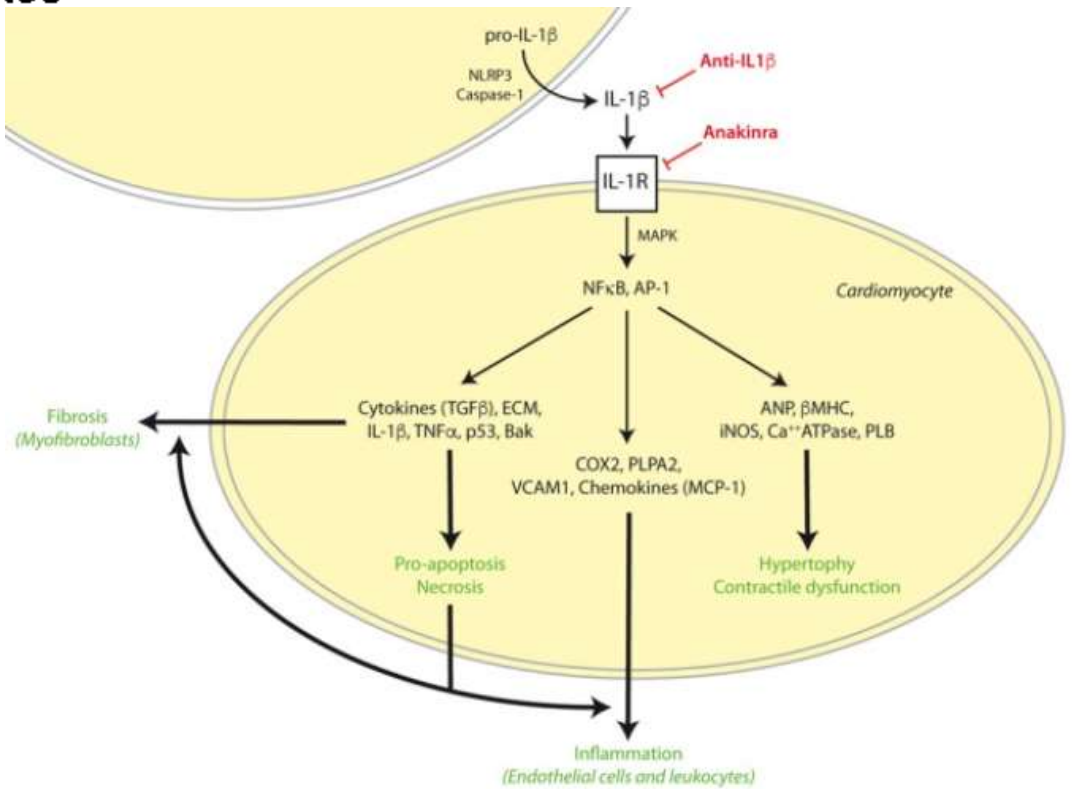


Marc Y. Donath et al, Nature Reviews Immunology (2019)
Yachana Kataria et al , Seminars in Immunopathology 2019

IL-1 and CV RISK



Disfunzione vascolare IL-1-mediata e sua inibizione da parte di IL-1Ra anakinra. Nelle cellule muscolari lisce vascolari (VSMC), IL-1β sinergizza con il elevati livelli di glucosio extracellulare (HG) per esacerbare lo stimolo pro-infiammatorio.

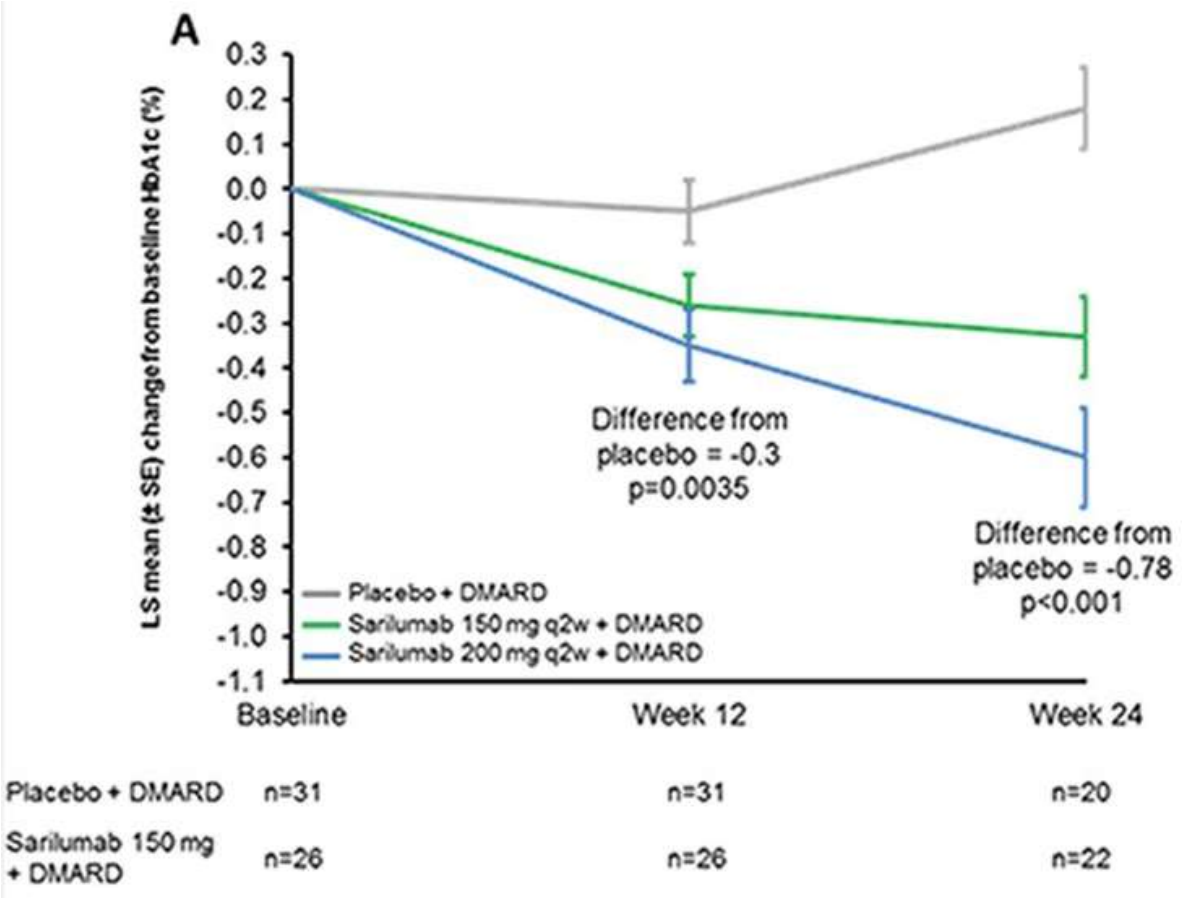


Attivazione di IL-1β nel danno cardiaco. Dopo un danno cardiaco come AMI o I / R, l'esacerbata espressione di IL-1β può indurre l'attivazione di NFκB e AP-1 e il conseguente aumento dei geni proipertrofici, contrattili, infiammatori, apoptosi / necrotici e fibrotici per le risposte autocrine e paracrine. Questi effetti sono rinforzati nel miocardio diabetico e possono essere stimolati dalla segnalazione di TNFa e TLR.

Concepción Peiró et al Front Pharmacol. 2017

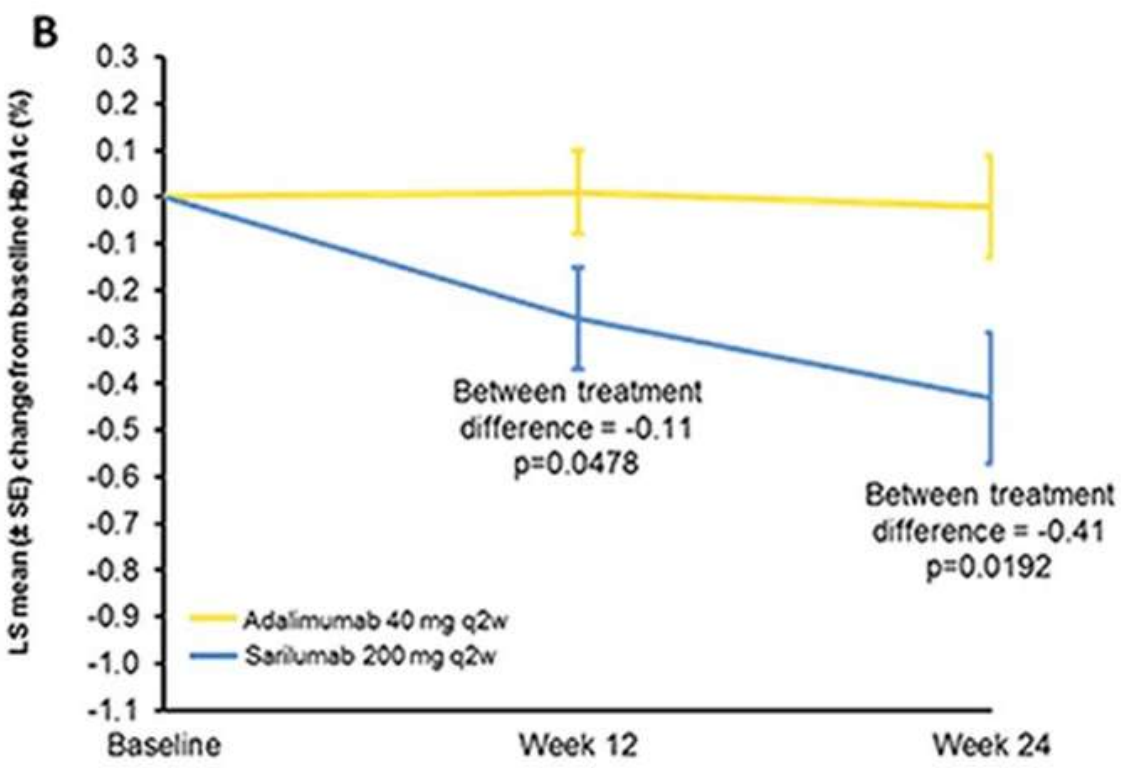
CHANGE IN HbA1c SARILUMAB-INDUCED

TARGET



Placebo + DMARD	n=31	n=31	n=20
Sarilumab 150 mg + DMARD	n=26	n=26	n=22

MONARCH

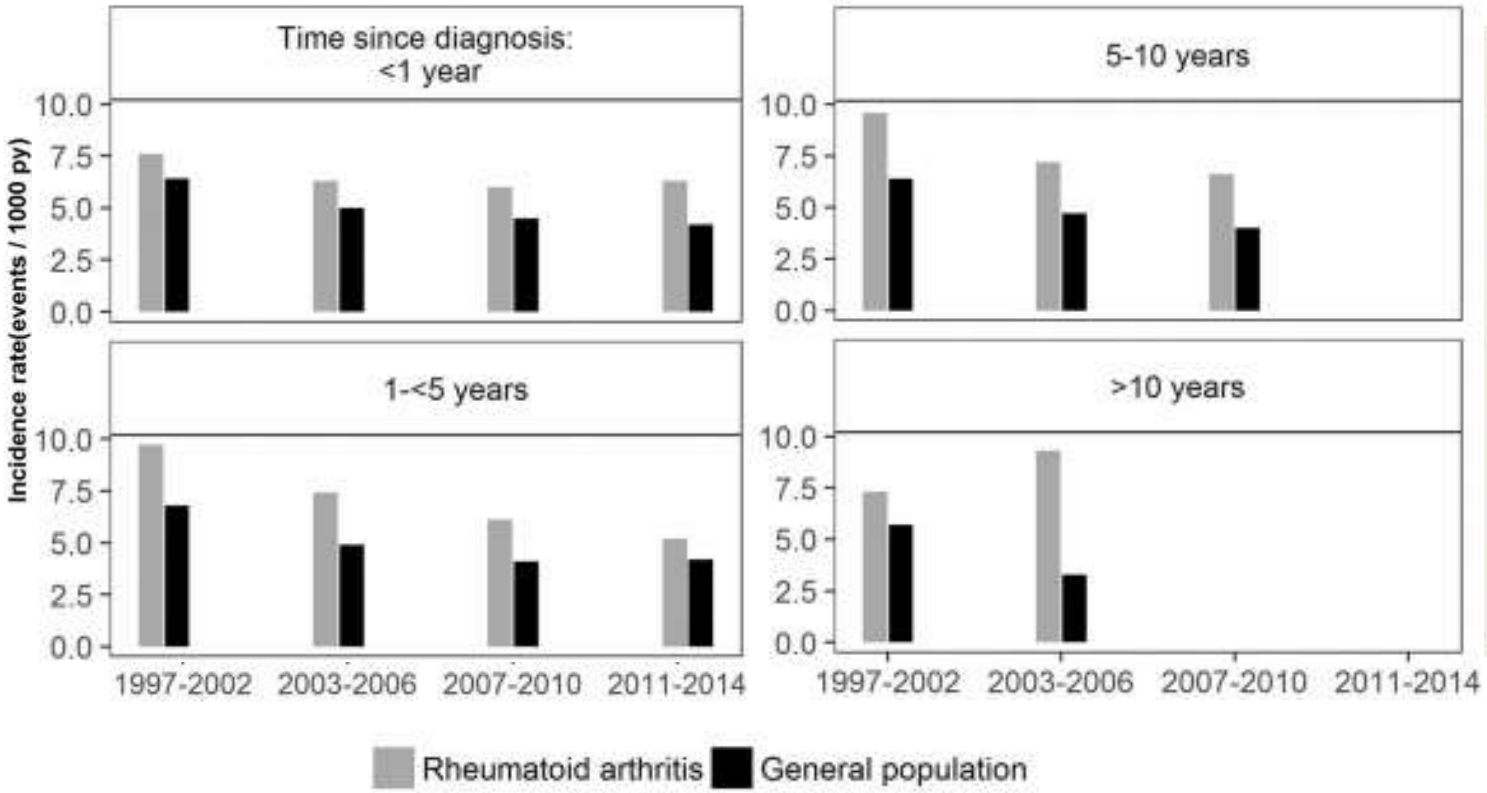


Adalimumab	n=17	n=16	n=14
Sarilumab	n=11	n=11	n=8

Reduction in HbA1c in patients with RA and diabetes (per ADA criteria: baseline fasting glucose ≥7 mmol/L or baseline HbA1c ≥6.5%; American Diabetes Association, Diabetes Care 2018;41(Suppl.1):S13-27

*Genovese MC, et al, Annals of the Rheumatic Diseases 2019;**78:**1128-1129.*

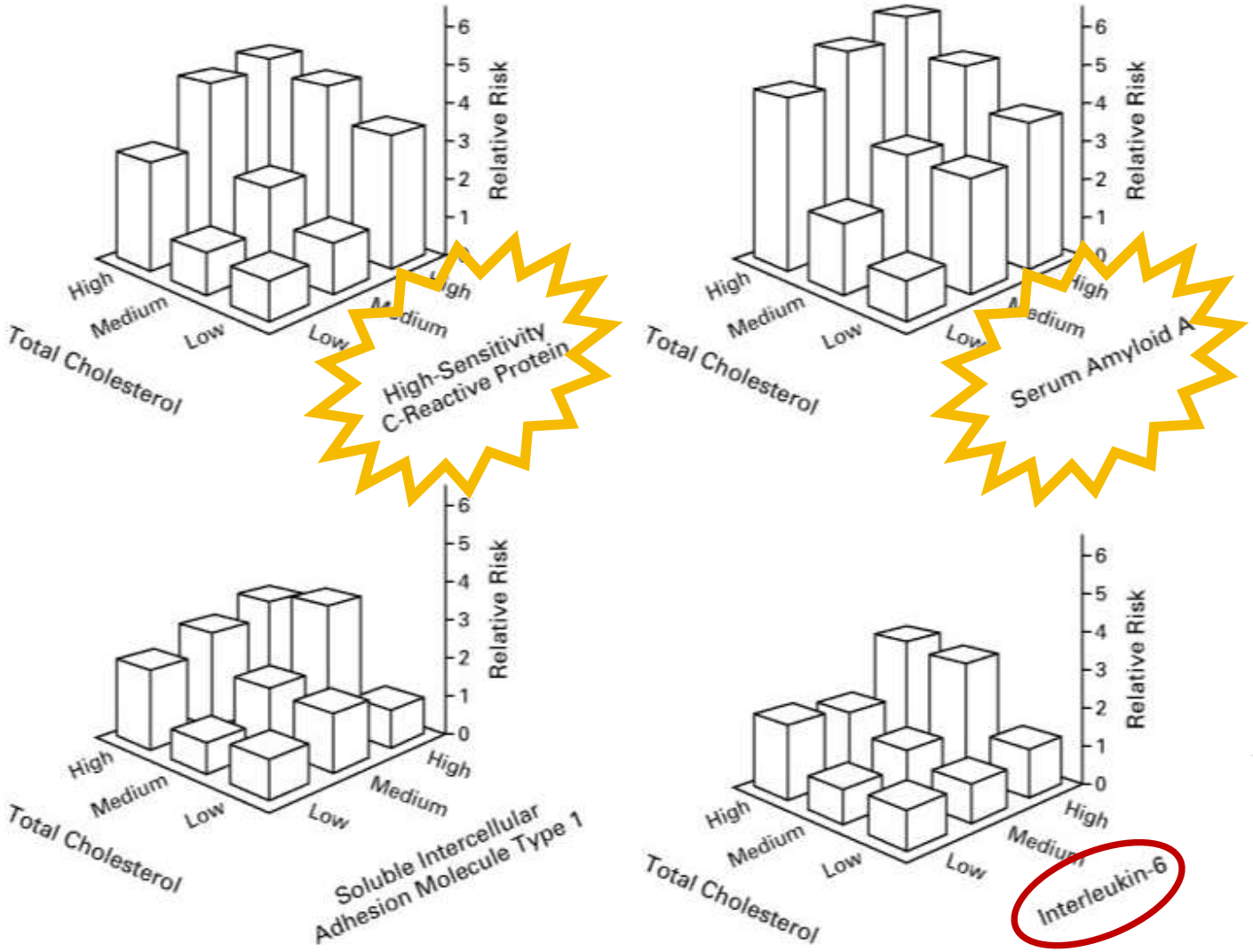
2016 EUROPEAN GUIDELINES ON CARDIOVASCULAR DISEASE PREVENTION IN CLINICAL PRACTICE

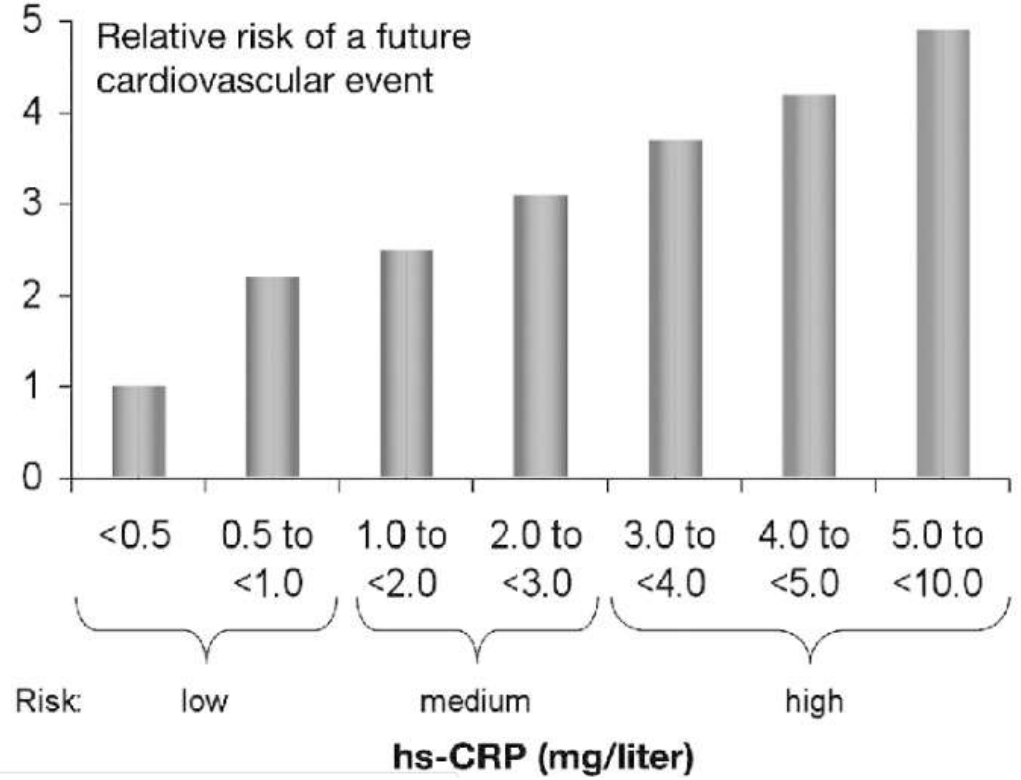


Recommendations	Class[a]	Level[b]	Ref[c]
The use of a 1.5 factor risk multiplier for CV risk in rheumatoid arthritis should be considered, particularly if disease activity is high.	IIa	B	177
The use of a 1.5 risk multiplier for CV risk in immune inflammatory diseases other than rheumatoid arthritis may be considered on a patient-by-patient basis, depending on disease activity/severity.	IIb	C	177

Piepoli M F et al, European Heart Journal (2016) 37, 2315–2381
Holmqvist M, et al. Ann Rheum Dis 2017;76:1642–1647

RA and CV-risk

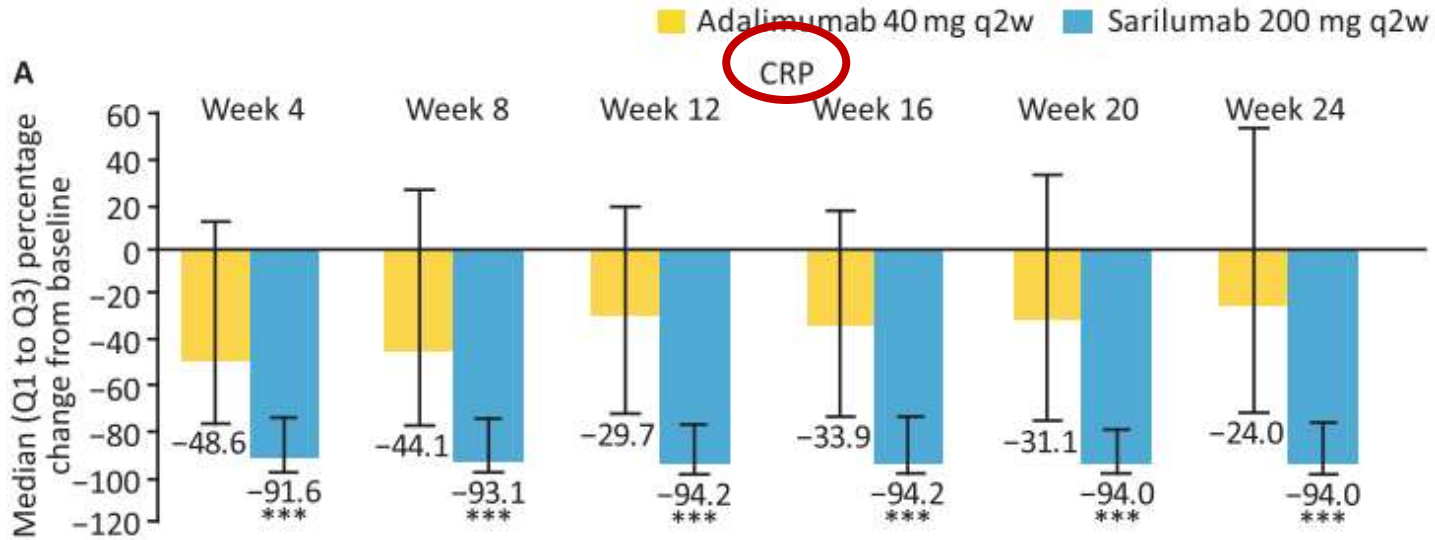


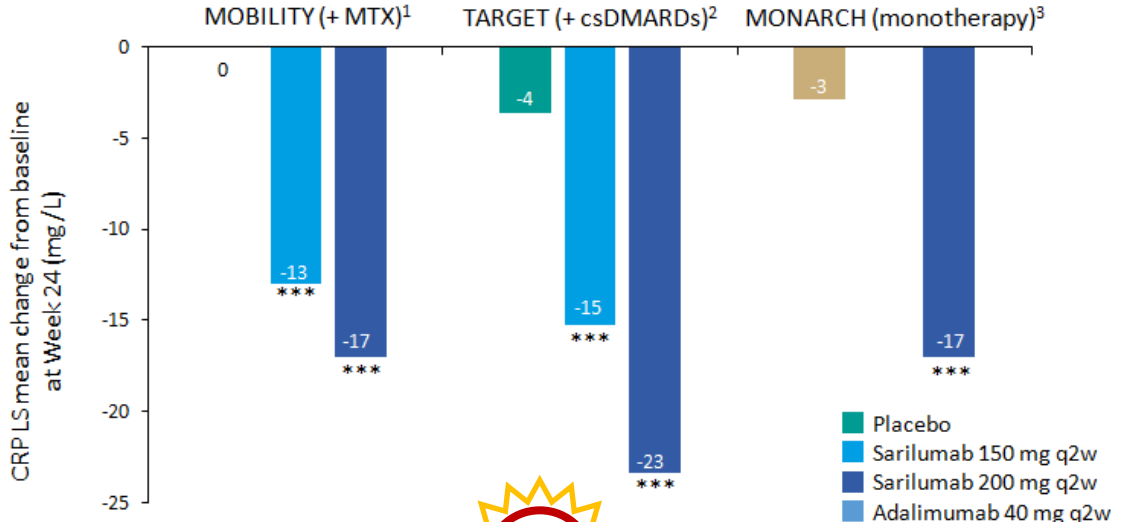


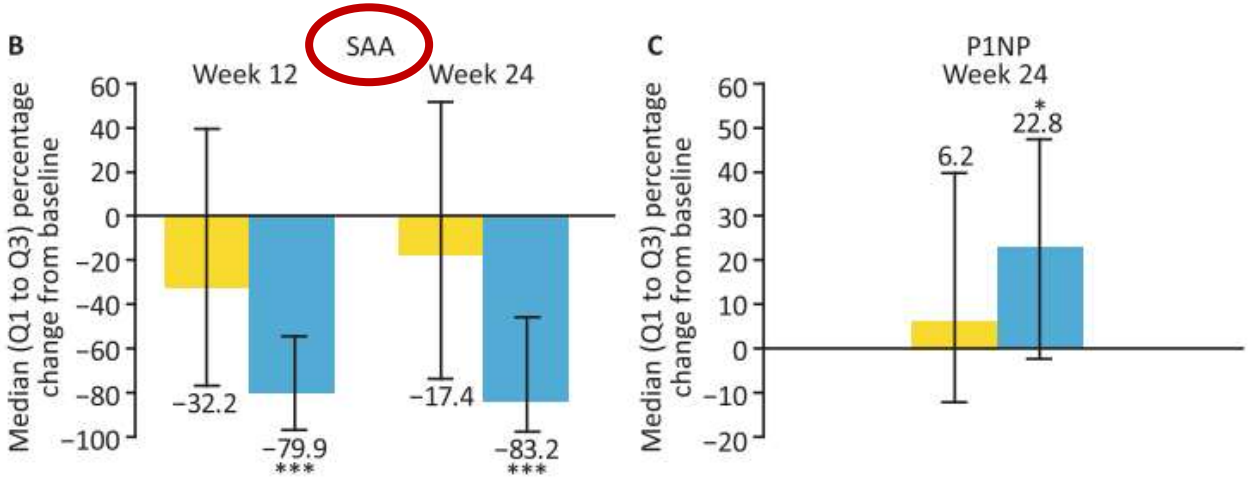
Relative Risk of Cardiovascular Events among Apparently Healthy Postmenopausal Women According to Base-Line Levels of Total Cholesterol and Markers of Inflammation.

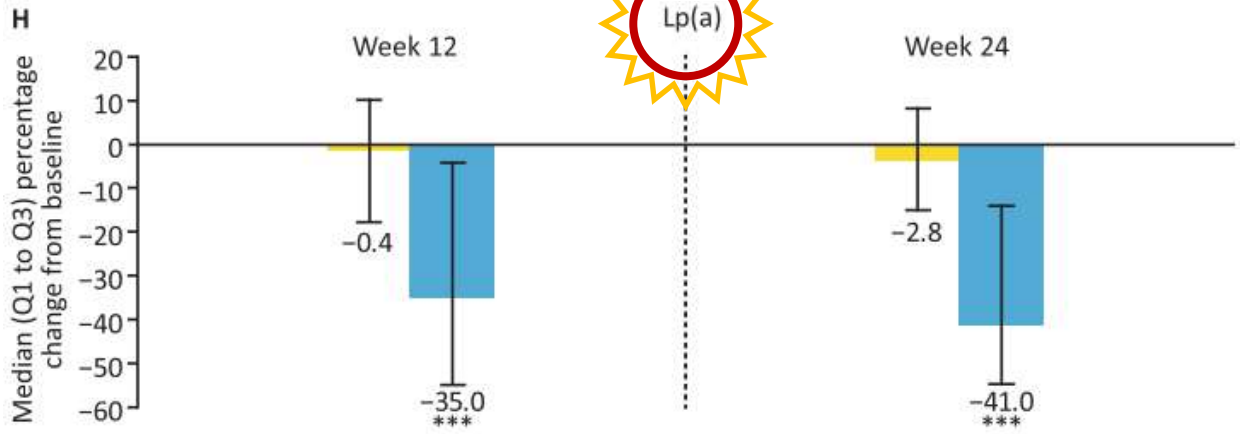
Ridker PM et al, N Engl J Med. 2000;342(12):836-843

SARILUMAB vs ADALIMUMAB – circulating biomarkers analysis





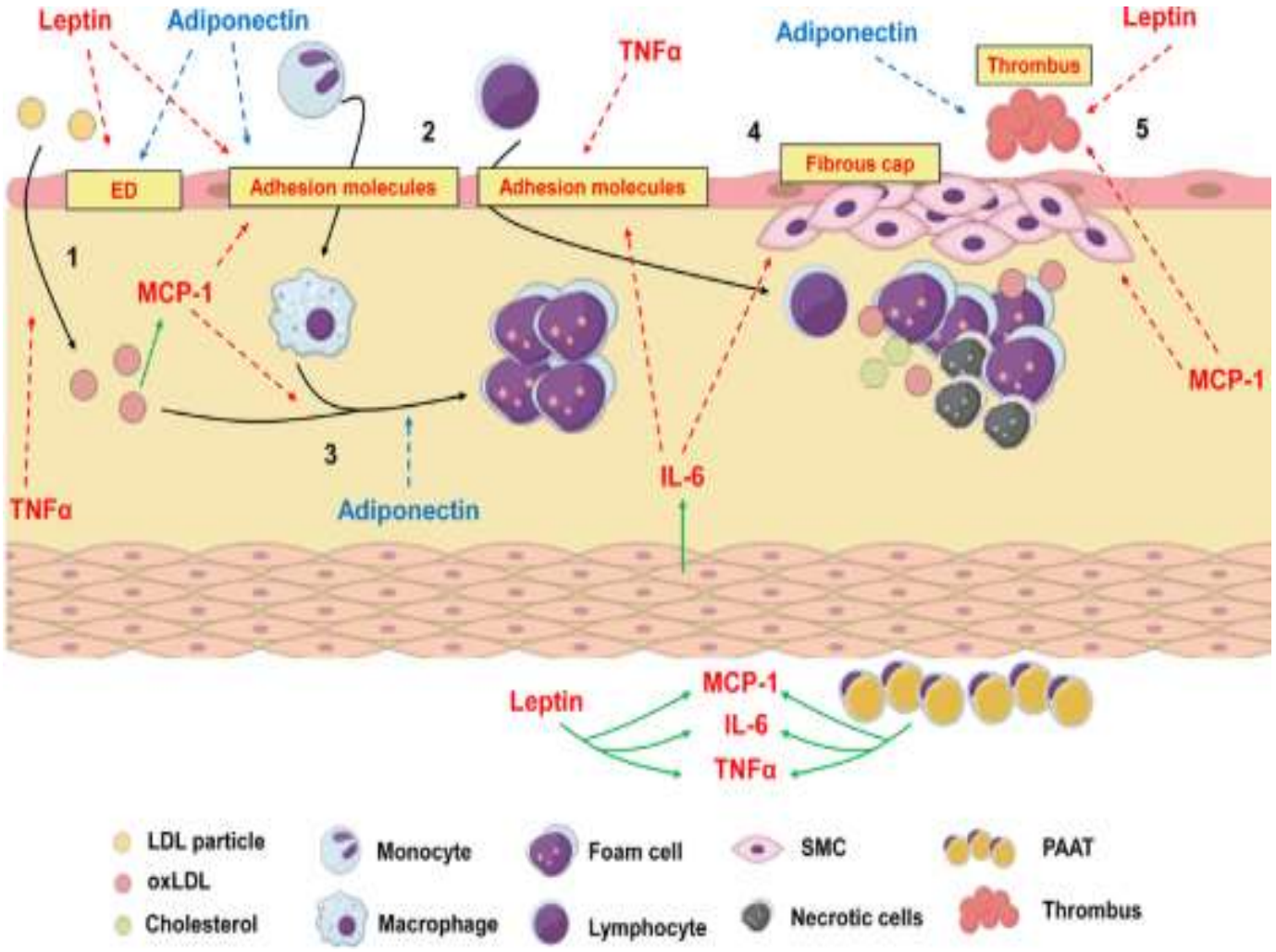




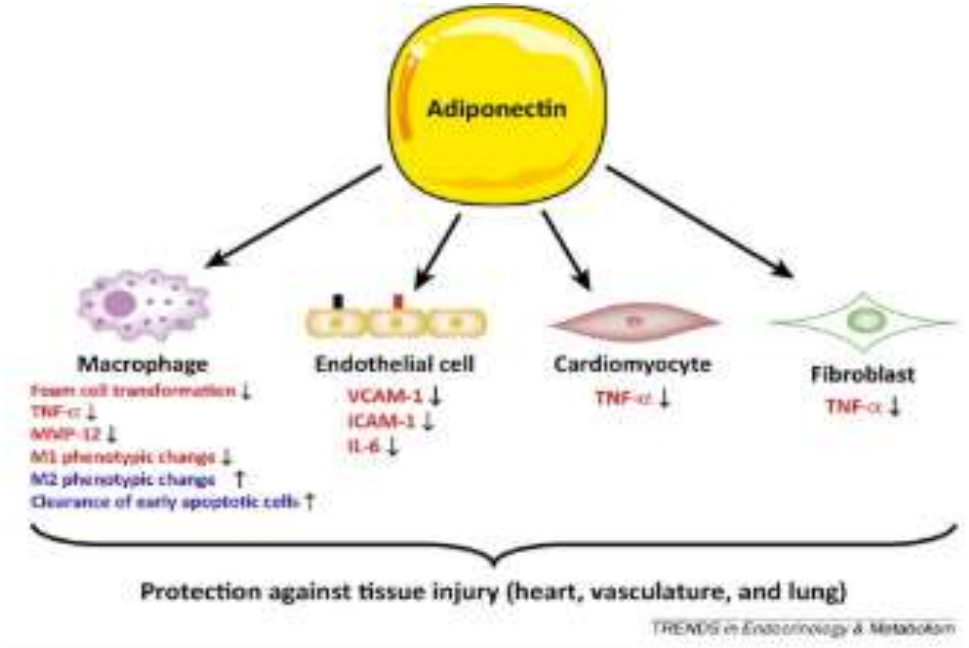
Median percentage changes from baseline in biomarkers through week 24

Gabay et al. Arthritis Research & Therapy (2020) 22:70 1. Genovese MC, et al. Arthritis Rheumatol 2015;67:1424–37 2. Fleischmann R, et al. Arthritis Rheumatol 2017;69:277–90; 3. Burmester G, et al. Ann Rheum Dis 2017;76:840–7.

TESSUTO ADIPOSO e REUMATISMI INFIAMMATORI



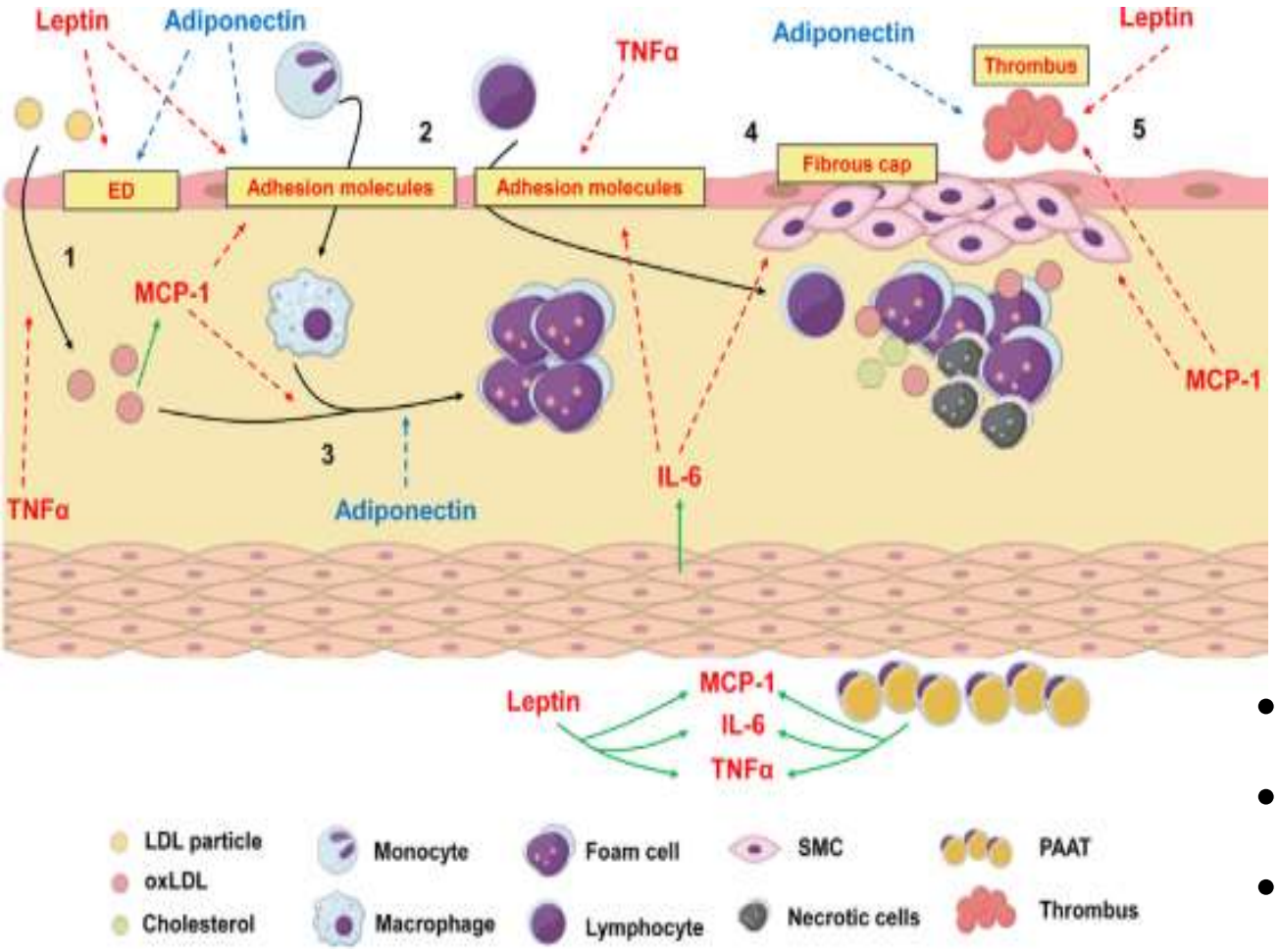
- Effetto anti-infiammatorio su endotelio e fagocitosi
- ↑ Citochine anti-infiammatorie: IL-10 e IL 1-RA
- Regola insulino-resistenza e protegge da aterosclerosi

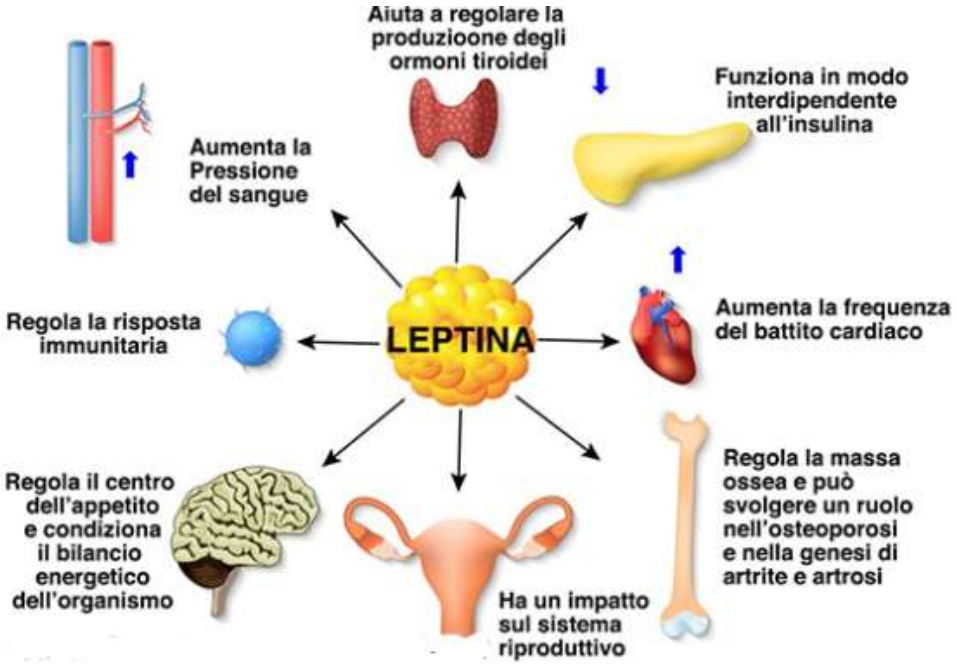


- Effetto pro-infiammatorio in AR (isoforma HMW)
- IL-6, VEGF e MMP-1/13 nei fibroblasti sinoviali, condrociti, cell endoteliali, linfociti
- Aumentata in liquido sinoviale in AR
- Livelli plasmatici correlano con s-PCR
- Associazione con progressione danno radiografico

Wolf et al. Biochem. Biophys. Res. 2004
Liu et al. Int Immunopharmacol. 2015
Cao et al. Autoimmunity 2016

TESSUTO ADIPOSO e REUMATISMI INFIAMMATORI





- Controlla appetito e spesa energetica
- Livelli sierici correlano con massa adiposa
- Effetti immunologici: ↑Th1, ↓Th2, ↑TNF-α, IL-6, IL-12, IL-2RA e recettore della transferrina a livello sinoviale ed endoteliale
- Up-regulation in pazienti con AR erosiva
  Associazione con durata di malattia e DAS-28

Lee et al. Z Rheumatol 2016
Tousirot et al. Life Sci. 2015

ALTRE ADIPOCHINE e AR

- **CHEMERINA:** Adipociti, liquido sinoviale, endotelio sinoviale in AR; Attività infiammatoria stimolata da TNF-α e INF-γ→ produzione sinoviale di IL-6, CCL2 e MMP-3; marker di attivazione endoteliale, angiogenesi e aterosclerosi in AR
- **RESISTINA:** tessuto adiposo e macrofagi attivati (IL-1, IL-6, TNF-α, LPS); insulino-resistenza; funzione endoteliale (↑ICAM-1); livelli sinoviali ↑ in AR
- **VISFATINA (Pre B-cell colony enhancing factor):** Leucociti→Tessuto adiposo viscerale; fibroblasti e macrofagi→↑IL-6, IL-8, MMP-1/3 e TNF-α; livelli sierici e sinoviali associati con s-FR, attività di malattia e progressione radiografica

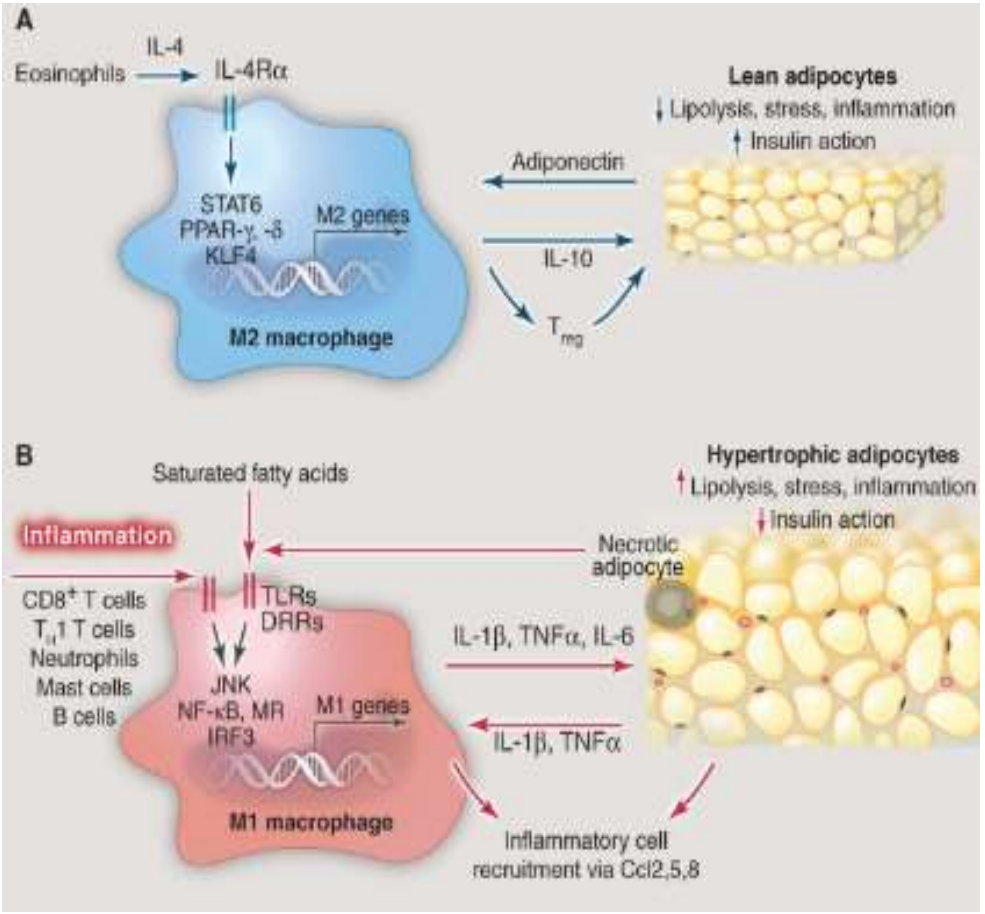
Carrión et al. Int J Mol Sci. 2019;
Lee YH et al. Int J Rheum Dis. 2018;
Mᵃᶜ Donald et al. Int J Mol Sci. 2019;
Fatel et al.Adv. Rheumatol 2018;
Tolusso et al. Expert Rev Clin Immunol. 2016

ALTERAZIONE DELL'ASSETTO LIPIDICO IN AR

- Dislipidemia precede manifestazioni cliniche
- Diminuzione paradossa di LDL in AR attiva
- TNF-alpha e IL-6 → foam-cells → piccole LDL ossidate o acetilate → ↑aterogenicità
- ↑HDL pro-infiammatorie (fibrinogeno, SAA ecc.)

OBESITA' E AR

- Neutrofili: ↑IL-8* articolare in topi early collagen-induced arthritis (CIA) obesi
- Macrofagi: ↑infiltrazione tissutale (M1) in obesità
- Linfociti T: ↑ nel grasso viscerale degli obesi→differenziazione TH-17 patogenica (IL-1, IL-6, IL-23)



Robertson et al. Nat. Rev. Rheumat 2013
Myasoedova et al. Ann. Rheum. Dis. 2010
Kim et al. Ann. Rheum. Dis. 2016;
Lee et al. Arch. Pharm. Res. 2013;
Endo et al. Mol. Life Sci. 2017

METABOLIC EFFECT OF RA THERAPY: altered adipokine levels and insuline sensitivity

- IFX ↓ resistina
- Anti-TNF ↑ adiponectina in alcuni studi
- = leptina
- ↓ Leptina/adiponectina (marker di resistenza all'insulina e s. metabolica) in corso di bDAMRDs
- DAMRDs+corticosteroidi nel primo trimestre migliora la sensibilità all'insulina e la dislipidemia
- Anti TNF ↑ sensibilità all'insulina

Kerekes, G. *et al. Nat. Rev. Rheumatol.* **10**, 691–696 (2014); published online 5 August 2014;

THE LANCET, OCTOBER 18, 1873.

ON THE

NERVOUS MIMICRY OF ORGANIC DISEASES,

Delivered at St. Bartholomew's Hospital,

BY SIR JAMES PAGET, BART., F.R.S.,
CONSULTING SURGEON TO THE HOSPITAL.

Annals of the Rheumatic Diseases 1997;56:326–329

Prevalence of low body mass in rheumatoid arthritis: association with the acute phase response

R Munro, H Capell

***Results*—13% of the RA group fell into the lowest 5th centile for BMI for the general population. The loss of body mass was greater for lean tissue than fat, with over 50% of the RA group falling into the lowest 10th centile of a reference population for the upper arm muscle area. Female patients who lost greater than 15% of their initial weight had higher health assessment questionnaire (HAQ) results than the rest of the group (p=0.020). In female patients there was a significant correlation between reduced fat free mass and the acute phase response (ESR p=0.016 and CRP p=0.003)**

***Conclusions*—There is an increased prevalence of low body mass, greatest for lean tissue, in the RA population. In the female group there was an inverse relation between the acute phase response and fat free mass. Female patients with RA who lose a significant amount of weight are more disabled as assessed by HAQ.**

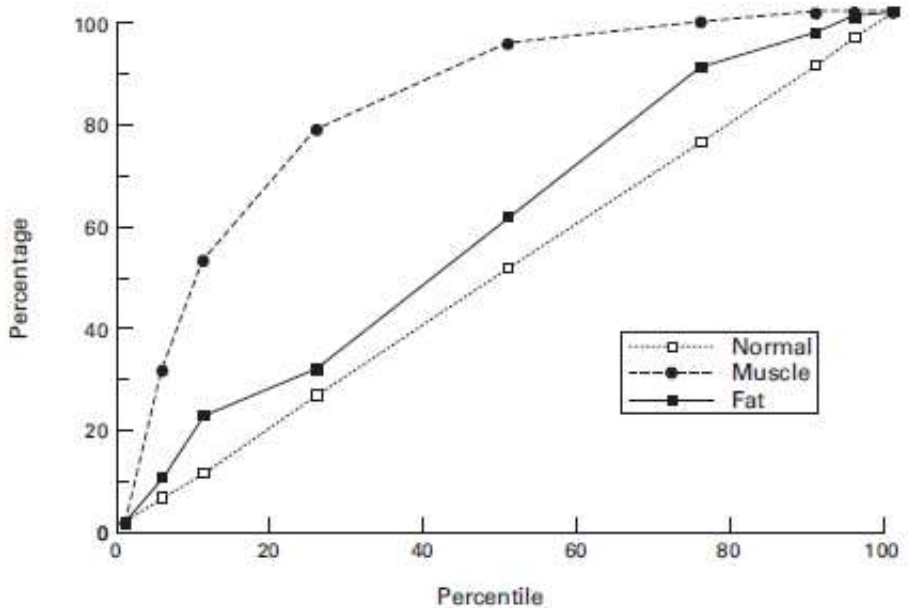


Figure 2 Arm muscle and fat area percentiles versus normal controls.

1/8 sottopeso vs 1/20

J Rheumatol. 1992 Oct;19(10):1505-10.

Rheumatoid cachexia: depletion of lean body mass in rheumatoid arthritis. Possible association with tumor necrosis factor.

Roubenoff R[1], Roubenoff RA, Ward LM, Holland SM, Hellmann DB.

RESULTS: When compared to United States population norms, 16 of the subjects (67%) were cachectic. In regression models, lean body mass (LBM) was inversely associated with the number of swollen joints ($p < 0.025$). Elevated TNF-alpha was found in 3 of 5 flaring patients vs 0 of 18 patients with less active disease ($p = 0.001$). These 3 were all cachectic, while the 2 flaring patients without detectable TNF had normal LBM ($p < 0.03$). Among the whole group, there was a trend toward increasing disability with decreased LBM after adjusting for joint pain and disease duration ($p < 0.07$).

J Clin Invest. 1994 Jun;93(6):2379-86.

Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation.

Roubenoff R[1], Roubenoff RA, Cannon JG, Kehayias JJ, Zhuang H, Dawson-Hughes B, Dinarello CA, Rosenberg IH.

Editorial

Rheumatoid cachexia: a complication of rheumatoid arthritis moves into the 21st century

Ronenn Roubenoff[1,2]

Loss of fat-free mass and higher fat mass are each associated with greater disability in RA [7], and low body weight (that is, both fat and fat-free tissue) in patients with RA is associated with threefold higher mortality [8]. Thus, rheumatoid cachexia may be an important contributor to increased morbidity and premature mortality in RA.

For example, the inflammatory cytokines tumor necrosis factor (TNF)-α and IL-1β are centrally involved in the pathogenesis of RA, but, in addition, these cytokines exert a powerful influence on whole-body protein and energy metabolism. Other sarcoactive molecules include IL-6, IFN-γ, transforming growth factor-β1, and MyoD

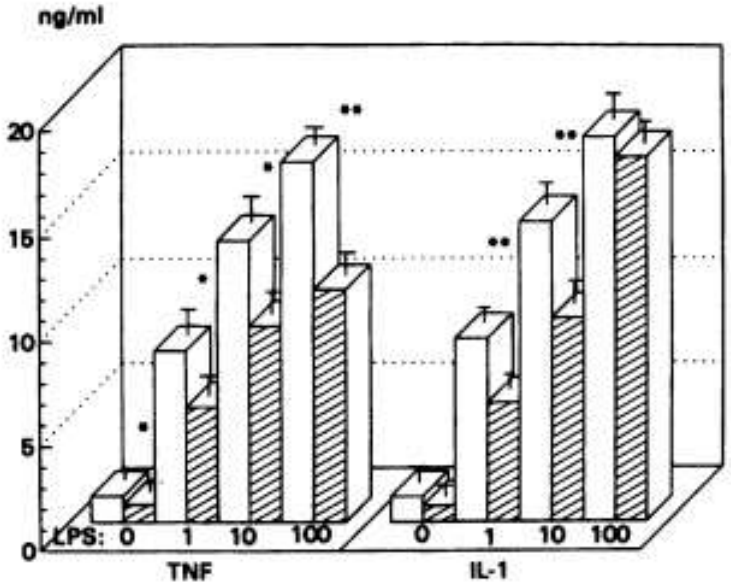


Figure 2. Production of TNF-α (*left*) and IL-1β (*right*) in subjects with RA (*open bars*) and in controls (*hatched bars*) with increasing concentration of LPS (nanograms per milliliter). Significant differences between RA and control cells were seen for TNF at all four levels of stimulation and for IL-1 at 1 and 10 ng LPS only. $*P < 0.05$; $**P < 0.01$.

Blockade of tumour necrosis factor-α in rheumatoid arthritis: effects on components of rheumatoid cachexia

G. S. Metsios[1–3], A. Stavropoulos-Kalinoglou[1,2], K. M. J. Douglas[2], Y. Koutedakis[3], A. M. Nevill[1], V. F. Panoulas[2], M. Kita[2] and G. D. Kitas[1,2]

TABLE 2. Mean ± S.D. and differences in the studied body composition and disease-related variables between the three different times of assessment

	Baseline	Time-1 (2 weeks)	Time-2 (12 weeks)	P
Body composition assessment				
Weight (kg)	79.4 ± 15.6	80.4 ± 16.2	78.8 ± 16.6	>0.05
BMI (kg/m^2)	28.3 ± 3.7	28.6 ± 3.8	28.1 ± 4.1	>0.05
Total body fat (%)	38.8 ± 7.5	36.5 ± 6.9	36.0 ± 7.4	>0.05
Truncal fat (%)	35.9 ± 6.7	37.4 ± 6.3*	36.7 ± 6.4	0.036
FFM (kg)	50.9 ± 12.7	50.5 ± 12.4	51.1 ± 12.5	>0.05
RA-related assessments				
CRP (mg/l)	33.7 ± 34.4	17.7 ± 11.9	15.3 ± 18.9	>0.05
ESR (mm/1st h)	41.7 ± 25.6	22.1 ± 16.9**	18.3 ± 15.4**	0.002
HAQ	1.83 ± 0.3	1.54 ± 0.3**	1.41 ± 0.4**	<0.001
DAS28	5.66 ± 0.7	4.64 ± 0.6**	3.59 ± 0.7**	<0.001
TNF-α (pg/ml)	38.1 ± 41.1	22.2 ± 26.8	8.9 ± 10.2*	0.024

P = level of significance between times of assessment using repeated-measures ANOVA. Difference from baseline assessment: **$P < 0.001$ and *$P < 0.05$.

Dopo 12 settimane di terapia anti-TNF nessun cambiamento significativo nel RRE (dispendio energetico a riposo) o nella FFM (massa muscolare magra).

Rheumatology 2007;46:1824–1827

Autoimmun Rev. 2014 Sep;13(9):981-1000. doi: 10.1016/j.autrev.2014.07.001. Epub 2014 Aug 2.

Obesity in autoimmune diseases: not a passive bystander.

Versini M[1], Jeandel PY[2], Rosenthal E[2], Shoenfeld Y[3].

relationship between obesity, adipokines - namely leptin, adiponectin, resistin, visfatin - and various immune-mediated conditions, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), multiple sclerosis (MS), type-1 diabetes (T1D), psoriasis and psoriatic arthritis (PsA), and thyroid autoimmunity (TAI), especially Hashimoto thyroiditis (HT). The strongest levels of evidence support an increased risk of RA (OR=1.2-3.4), MS (OR=2), psoriasis and PsA (OR=1.48-6.46) in obese subjects. A higher risk of IBD, T1D and TAI is also suggested.

Moreover, obesity worsens the course of RA, SLE, IBD, psoriasis and PsA, and impairs the treatment response of RA, IBD, psoriasis and PsA. Extensive clinical data and experimental models demonstrate the involvement of adipokines in the pathogenesis of these autoimmune diseases. Obesity appears to be a major environmental factor contributing to the onset and progression of autoimmune diseases.

L'OBESITÀ IN RA È STATA TROVATA PREVALENTE NEL 18-31% DEI PAZIENTI, NEL COMPLESSO LEGGERMENTE MAGGIORE RISPETTO ALLA POPOLAZIONE GENERALE. UNA CONDIZIONE DI SOVRAPPESO È STATA RILEVATA IN PIÙ DEL 60% NEI PAZIENTI RA

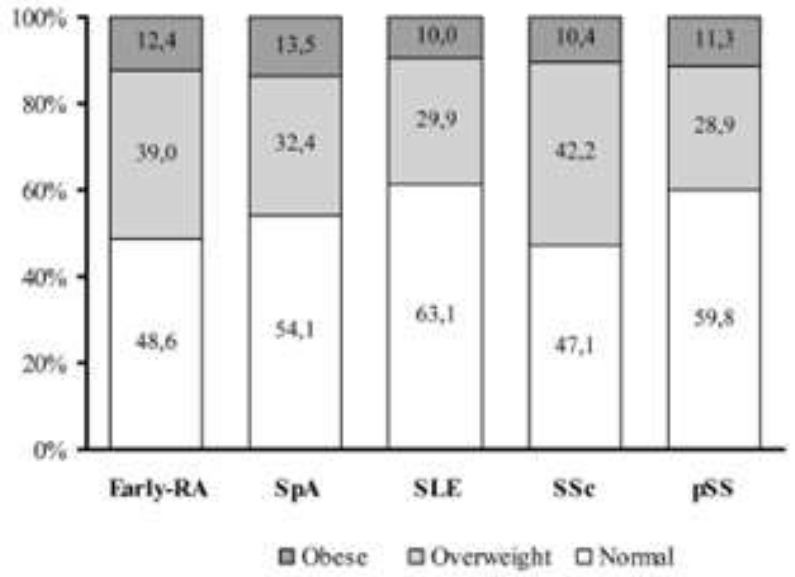
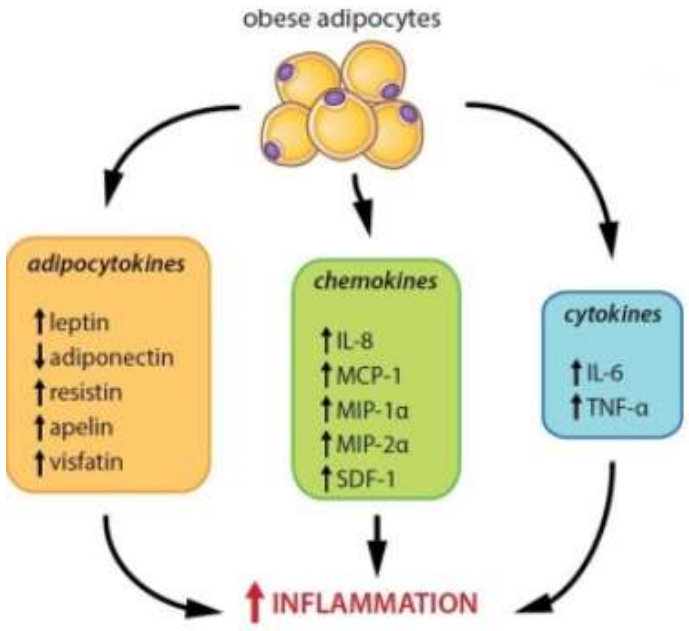


FIGURE 1 | Distribution of BMI categories among an Italian cohort of adult autoimmune disease patients

Gremese et al. Front Immunol. 2014; 5: 576.



Body mass index distribution in rheumatoid arthritis: a collaborative analysis from three large German rheumatoid arthritis databases

Table 2 Distribution of the body mass index (BMI) by sex and age groups (%)

Cohort	BMI (kg/m^2)	Females				Males			
		40– < 55	55– < 70	≥70	Total	40– < 55	55– < 70	≥70	Total
CAPEA	<18.5	1.0	1.0	2.9	1.4	0.9	0.8	0	0.6
	18.5 to <25	40.4	34.2	33.1	36.3	35.7	24.8	32.0	30.6
	25 to <30	32.7	34.6	42.5	35.8	43.8	52.0	45.0	47.2
	≥30	26.0	30.2	21.6	26.5	19.6	22.4	23.0	21.7
RABBIT	<18.5	2.6	1.7	2.0	2.1	0.5	0.7	0.5	0.6
	18.5 to <25	43.2	37.2	38.2	39.6	30.0	27.2	33.9	29.3
	25 to <30	29.8	35.3	36.8	33.6	45.5	46.7	49.9	46.8
	≥30	24.4	25.8	23	24.8	24	25.3	15.8	23.3
NDB	<18.5	2.0	1.2	2.4	1.8	1.0	0.3	0.7	0.6
	18.5 to <25	48.9	40.6	40.8	42.8	35.4	25.4	34.8	31.3
	25 to <30	26.0	34.3	36.5	33.0	43.9	49.8	48.4	47.8
	≥30	23.1	23.9	20.3	22.4	19.7	24.4	16.0	20.2
DEAS	<18.5	1.1	1.4	1.2	1.2	0.3	0.1	0.5	0.3
	18.5 to <25	54.9	43.4	36.7	45.7	34.4	26.9	28.6	29.8
	25 to <30	29.9	36.8	39.9	35.2	49.4	51.9	52.8	51.4
	≥30	14.1	18.4	22.2	17.9	15.9	21.1	18.2	18.5

i pz AR erano significativamente più obesi dei controlli

Albrecht *et al. Arthritis Research & Therapy* (2016) 18:149
DOI 10.1186/s13075-016-1043-9

BioMed Research International
Volume 2019, Article ID 3579081, 12 pages
https://doi.org/10.1155/2019/3579081

Medicine • Volume 95, Number 8, February 2016

• in presenza di fattori di rischio le donne obese hanno una più elevata probabilità di sviluppare AR

• in particolare se BMI>30 e sieronegative per ACPA

• nel gruppo obeso vi era minore probabilità di raggiungere una remissione, il mantenimento della remissione indipendentemente dall'uso di DMARDs, steroidi e bDMARDs

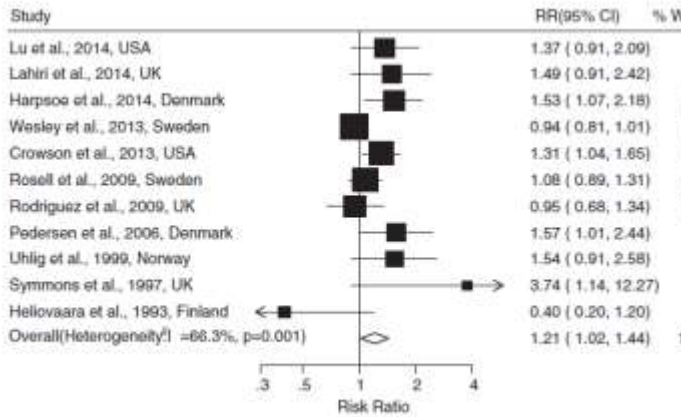


FIGURE 2. Adjusted relative risks of rheumatoid arthritis for obesity compared to normal weight.

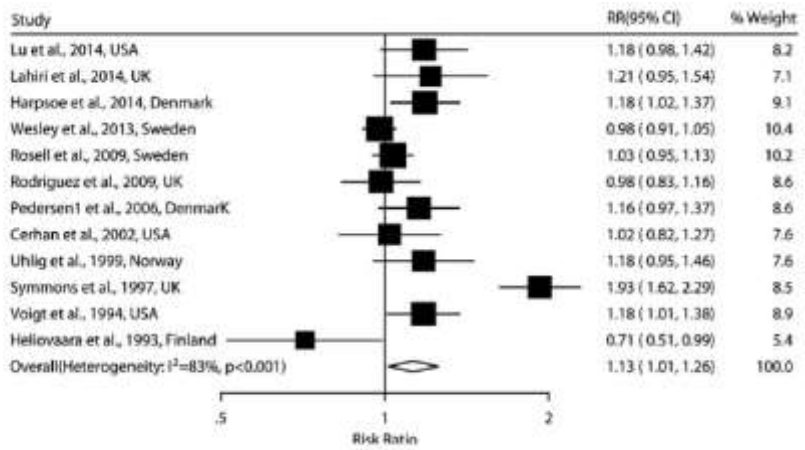


FIGURE 4. Adjusted relative risks of rheumatoid arthritis for every 5 kg/m^2 increase in body mass index.

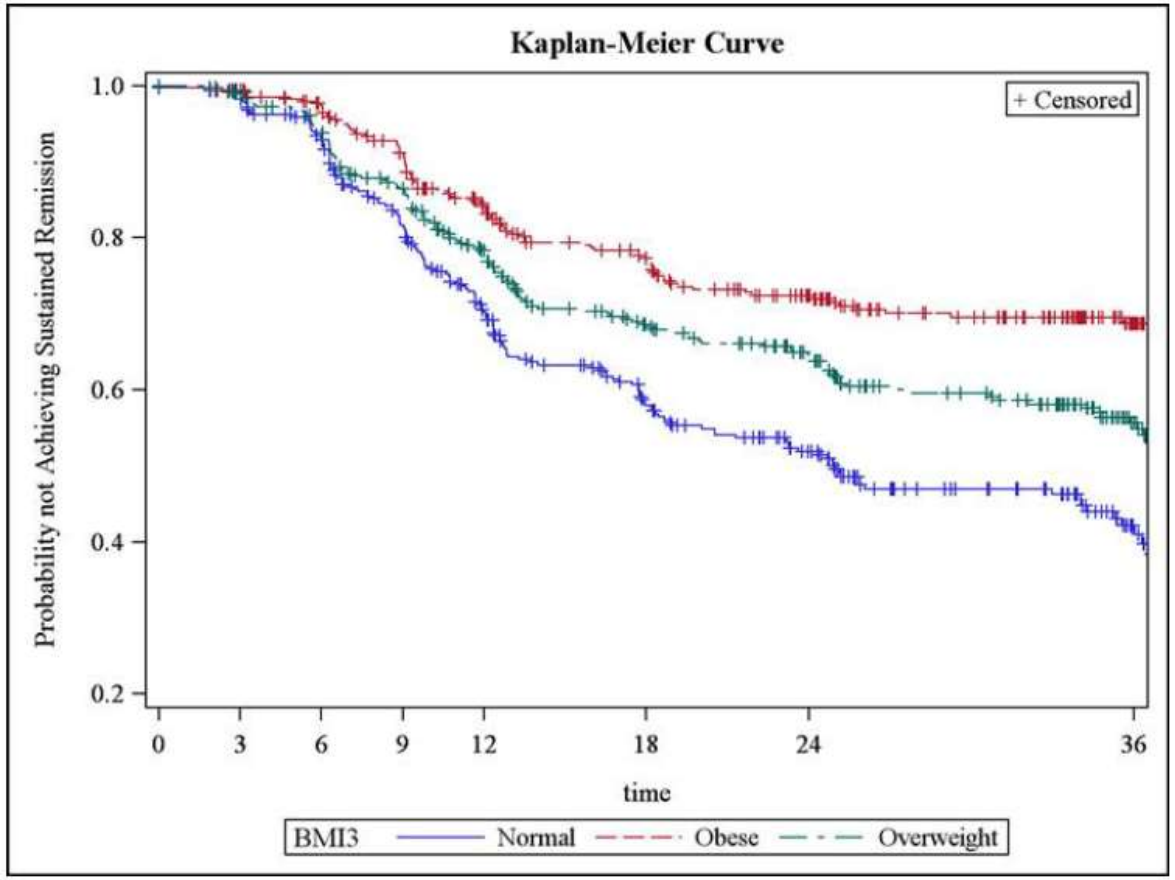
High Body Mass Index Negatively Impacts Time to Achieving Sustained Remission in Early Rheumatoid Arthritis: Results from a Multicenter Early Arthritis Cohort Study

TABLE 1: Multivariate Analysis about the Relationship between Time to Sustained Remission and the Variables of Interest using Cox Regression*

Hazard ratio Estimate				
Parameter	Point Estimate	95% Confidence Interval		p-value
BMI Overweight vs Normal	0.75	0.59	0.97	**0.03**
BMI Obese vs Normal	0.63	0.48	0.82	**0.0008**
HAQ-DI	0.81	0.65	1.01	0.06
Pain (0-10)	0.99	0.94	1.04	0.74
DAS28<3.2 by 6 months (Yes vs No)	4.21	3.33	5.32	**<0.0001**
Age	1.00	0.99	1.00	0.22
Gender (Female vs Male)	0.80	0.63	1.00	0.07
Ethnicity (Non-Caucasian vs Caucasian)	0.72	0.51	1.02	0.06
Education >high school	1.61	1.00	2.58	**0.05**
Never/Ex smoker	1.35	0.99	1.84	0.06
Symptom Duration	1.00	1.00	1.00	0.88
CRP	1.01	1.00	1.01	0.14
Number of co-morbidities	0.91	0.09	0.98	**0.007**
MTX 1st 3 months	1.40	1.05	1.87	**0.02**
Steroids 1st 3 months	0.76	0.61	0.95	**0.01**

pz obesi e sovrappeso hanno minore probabilità di raggiungere remissione sostenuta rapidamente così come PDN nel primo trimestre N elevato di comorbidità;

MTX primo trimestre, peso normale e DAS28 < 3.2 correlano con maggiore probabilità di remissione sostenuta



Arthritis Rheumatol. 2015; 67 (suppl 10).

Ann Rheum Dis. 2008 Jun;67(6):769-74. Epub 2007 Oct 26.

A high body mass index has a protective effect on the amount of joint destruction in small joints in early rheumatoid arthritis.

RESULTS: Obesity did not influence the likelihood of developing RA. In both RA cohorts, the BMI was inversely correlated with the Sharp-van der Heijde score after 3 years' follow-up ($r = -0.15$, $p = 0.025$ for the Leiden EAC and $r = -0.27$, $p<0.001$ for the replication cohort). Linear regression analyses in both cohorts showed that the BMI was independently and inversely associated with the level of joint destruction in anti-CCP-positive patients with RA, but not in anti-CCP-negative patients.

The Association of Body Mass Index (BMI) and Radiographic Progression of Joint Disease in Rheumatoid Arthritis (RA)

Association of BMI and radiologic progression of joint disease in RA

Multivariate Logistic Regression Model*	Odds Ratios	Confidence Intervals
BMI (underweight vs. Obese)	**4.85**	**1.34-17.53****
BMI (Normal vs. Obese)	**3.99**	**1.76-9.05**
BMI (Overweight vs. Obese)	1.65	0.68-4.02
DAS28-CRP4 (continuous)	**1.28**	**1.08-1.51**
Anti-CCP Positive	1.85	0.96-3.57

*adjusted for age and gender

**test for trend of BMI group and radiologic progression p=0.0006

Pz sottopeso e normo peso ↑ probabilità di progressione radiografica

Examining the Obesity Paradox in Patients With Rheumatoid Arthritis

Linda Peckel

Having a high BMI [body mass index] may increase the likelihood of developing RA in those who are genetically susceptible, and decrease the likelihood of achieving sustained remission for those with active RA

At the same time, however, patients with obesity also have a lower risk for mortality from RA than patients of normal weight. In what is widely known as the "obesity paradox," patients with RA with a BMI >30 kg/m^2 live longer than patients with BMI <30 kg/m^2.[1,2]

this paradox may be due to *rheum cachexia*, whereby the ratio of fat to lean body mass is altered by RA disease activity.

there is a clear effect on damage mediated through impact and weight that can accelerate joint damage

Weight Loss, the Obesity Paradox, and the Risk of Death in Rheumatoid Arthritis

Rate of change in BMI over the previous interval and risk of subsequent d

Rate of change in BMI (no. of observations)	Risk of death	*P*
No weight loss (8,000)	1 (reference)	
0–<2 kg/m^2 loss/year (6,541)	1.12 (0.85–1.49)	0.4
2–3 kg/m^2 loss/year (1,067)	1.65 (1.09–2.50)	0.02
>3 kg/m^2 loss/year (1,421)	2.49 (1.73–3.57)	<0.001

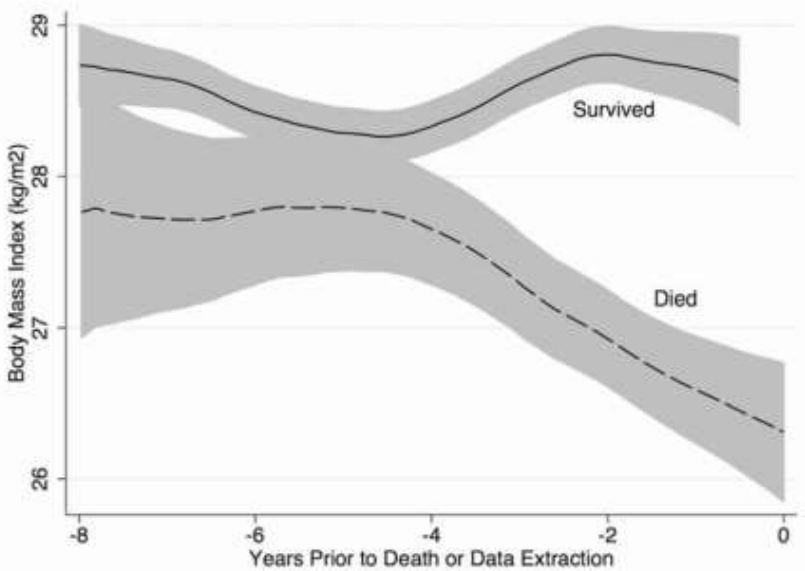


Figure 1.
Lowess curve illustrating the mean body mass index and 95% confidence interval prior to the date of death in patients who died compared with those who survived to the date when the database was queried.

Arthritis Rheumatol. 2015 July ; 67(7): 1711–1717. doi:10.1002/art.39136.

Rheumatoid arthritis and metabolic syndrome

Kerekes, G. *et al. Nat. Rev. Rheumatol.* **10**, 691–696 (2014); published online 5 August 2014;

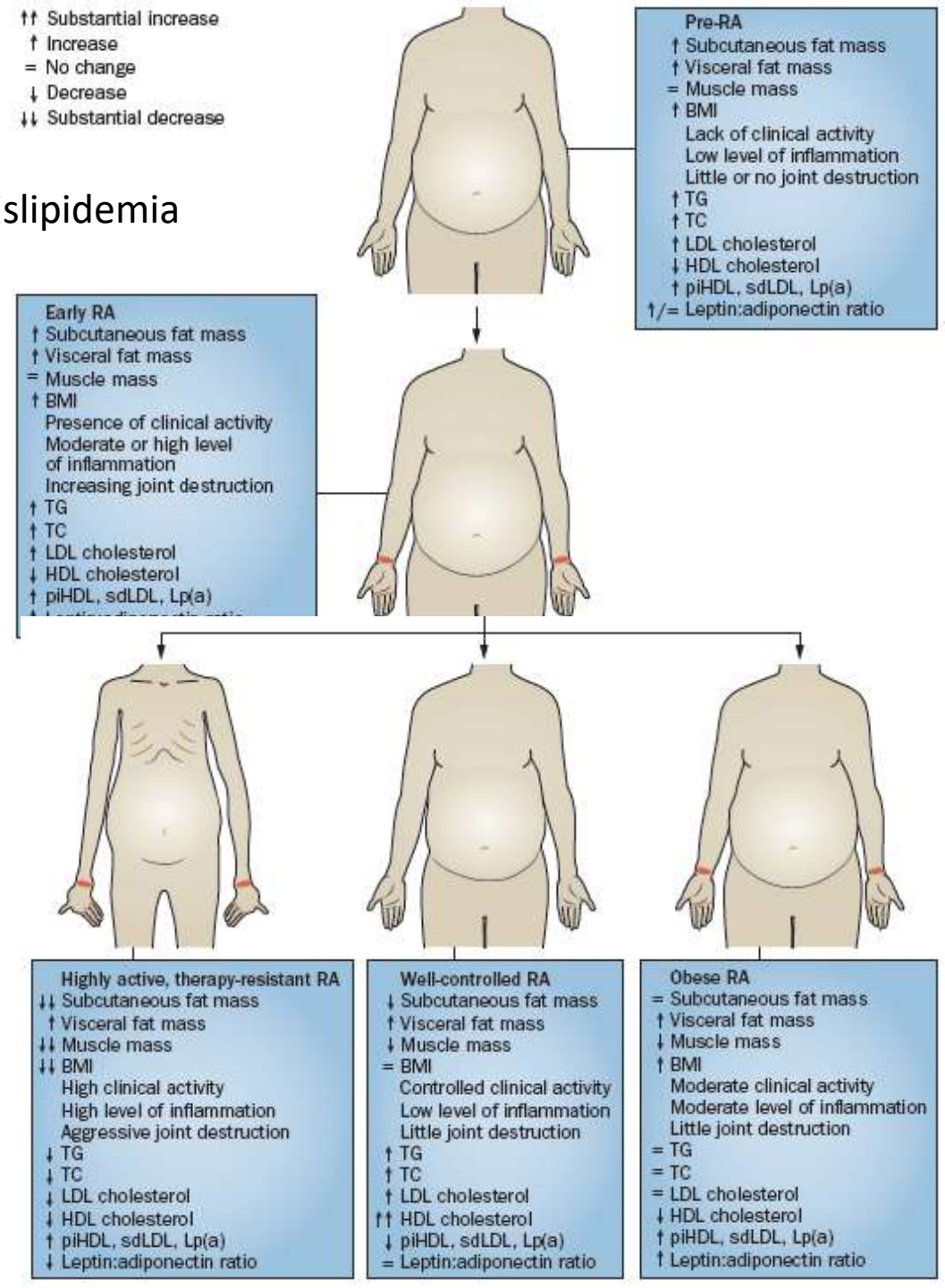
↑circonferenza vita , IA, alterata glicemia a digiuno o insulino-resistenza e dislipidemia

ALTERAZIONI QUANTITATIVE

- AR preclinica e early: profilo tipico della sindrome metabolica (Col tot =/↑; LDL e TGD ↑, HDL ↓)
- AR consolidata: ↓ grasso bianco s.c., ↑ grasso viscerale
- AR attiva: ↓ LDL e colest tot

ALTERAZIONI QUALITATIVE

- Modifiche fenotipiche LDL → Lipoteina (a), una particella LDL legata all'apolipoproteina A, è un fattore di rischio moderato indipendente per CVD (più sensibili a stress ox) che risulta ↑ ↑ nei pz AR.
- Alterata distribuzione delle subfrazioni HDL con ↑HDL2 da iper TGD e ↓HDL3 a aumentata clearance; pro-infiammatorie
- Alterazioni della funzione HDL: difesa dell'ospite vs funzione metabolica
- ↓ potere anti-ox



Kerekes, G. *et al. Nat. Rev. Rheumatol.* **10**, 691–696 (2014); published online 5 August 2014;

Table 1 | Independent effects of various RA-related factors on lipid levels

Factor	Cholesterol			Triglycerides	References
	Total	LDL	HDL		
Patient-related					
Obesity and/or metabolic syndrome	↑	↑	↓	↑	6,8,11,15,18,20
Sedentary lifestyle	↑	↑	↓	↑	6,8,18
Ageing	↓	↓	↑	↓	8
Smoking	=	=	↓	=	8
Disease-related					
Acute high-grade inflammation	↓ or =	↓ or =	↓	↑	1,6,8,23,51
Chronic high-grade inflammation	↓	↓	↓	↓	6,8,23,51
Rheumatoid cachexia	↓	↓	↓	⇊	6,11,12,15,16
Treatment-related					
High-dose, long-term corticosteroids	↑	↑	↓	↑	6,8
Low-dose corticosteroids	=	=	↑	=	6,8
Methotrexate	↑ or =	↑ or =	↑	=	8,29,49
Sulphasalazine	↑	=	↑	=	8,29,49
Hydroxychloroquine	↓ or =	↓ or =	↑ or =	↓ or =	8,49
Biologic therapies	↑	↑	↑	↑	6,8,10,39,45,46,48,50

Abbreviations: =, no change; ↑, increase; ↓, decrease; ⇊ substantial decrease; RA, rheumatoid arthritis.

Kerekes, G. *et al. Nat. Rev. Rheumatol.* **10**, 691–696 (2014); published online 5 August 2014;

METABOLIC EFFECT OF RA THERAPY: rheumatoid cachexia and obesity

TNF-i

Rheumatoid cachexia can persist in patients receiving biologic therapy even after the improvement of arthritis symptoms. In a study of 20 patients with RA and 12 healthy individuals, anti-TNF therapy in the RA group resulted in an improvement of physical activity and protein intake but not in energy expenditure or lean body mass.[44] Further prospective studies in this field are needed.

Treatment with anti-TNF agents and other biologic therapies may result in elevations of lipid subfractions

Indeed, some investigators reported that although short-term anti-TNF treatment increased lipid fractions (including total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol levels), the atherogenic index—defined as the total cholesterol:HDL cholesterol ratio—remained unchanged.[23,45]

IL-6 & JAK-i

Particularly pronounced increases in circulating lipid levels have been associated with the anti-IL-6R antibody tocilizumab and the Janus kinase inhibitor tofacitinib.[23,47] However, according to the lipid paradox, the elevations in lipid levels observed during treatment with these agents, as well as with anti-TNF biologic therapies, might reflect their potent suppressive effects on CRP.[7,8,23]

ApoB:ApoA1 ratio, a biomarker used for CVD risk stratification, remained unchanged in most treated patients with RA.[46]

Kerekes, G. *et al. Nat. Rev. Rheumatol.* **10**, 691–696 (2014); published online 5 August 2014;

Joint Bone Spine. 2019 Mar;86(2):173-183. doi: 10.1016/j.jbspin.2018.03.007. Epub 2018 Apr 7.

Impact of obesity on the efficacy of different biologic agents in inflammatory diseases: A systematic review and meta-analysis.

Shan J[1], Zhang J[2].

Table 1
Characteristics and main findings of included studies: obesity and clinical response to anti-TNF agents in AS or axSpA patients.

Refs	Patients			BMI timing	Therapy: anti-TNF agent (*n*)	Groups (*n*)			Reported outcomes				Clinical response was assessed by	Study design	
	Rheumatic disease (*n*)	Obese %	Female %			Obese	Over weight	Normal weight	Clinical response			Other		Type of study	Duration (months)
Ottaviani et al. 2012 [26]	AS (155)	24.5	36.7	Baseline	IFX	38	54	63		BASDAI50 %[a]	BASDAI20 %[a]	BASDAI70 %[a]	BASDAI50 response rate (%) and BASDAI20%; BASDAI70%[a]	Retrospective cohort	6
									Obese[a]	26.5 %[a]	41.2 %[a]	5.9 %[a]			
									Overweight[a]	48.9%[a]	71.2%[a]	29.8%[a]			
									Normal weight[a]	77.6%[a]	84.5%[a]	48.3%[a]			
										P < 0.001[a]	*P* < 0.001[a]	*P* < 0.001[a]			
Rosas et al., 2017 [27]	AS (57)	26.3	35	At treatment	ADA (57)	15	25	17	Obese ↓ Achieving BASDAI ≤ 4 (*P* = 0.05) Achieving ASDAS ≤ 2.1 (*P* = 0.02)[a]			Blood ADL levels↓ *P* = 0.032 Anti-ADL Abp = 0.13[a]	BASDAI index and the ASDAS ESR index[a]	Cross-sectional study	–
Gremese et al. 2014 [28]	Axial SpA (170)	13.5	30.6	Baseline	IFX (104) ETA (31) ADA (35)	23	55	92	BASDAI50% Obese: 30.4%; Overweight: 54.5%; Normal weight: 72.8% *P* < 0.001[a]				BASDAI50 response rate (%)[a]	Retrospective cohort	12
Micheroli et al., 2017 [29]	Axial SpA (624)	14.1	37.8	Baseline	IFX (137) ADA (215) ETA (167) GOL (105)	88	204	332		ASAS40%[a]	BASDAI50%[a]	ASDAS < 2.1%[a]	BASDAI50 response rate (%) ASAS40 response rate (%) ASDAS ESR index[a]	Retrospective cohort	12
									Obese[a]	29%[a]	33%[a]	25%			
									Overweight[a]	34%[a]	40%[a]	41%			
									Normal weight[a]	44%[a]	48%[a]	56%			
										P = 0.02[a]	*P* = 0.06[a]	*P* < 0.001[a]			

AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; ASAS: Assessment in SpondyloArthritis International Society; ASAS40: 40% improvement according to ASAS; BASDAI: Bath ankylosing spondylitis disease activity index; BASDAI50: 50% improvement according to BASDAI; anti-TNF agents include infliximab (IFX), adalimumab (ADA), etanercept (ETA), certolizumab (CTZ) and golimumab (GOL).

[a] Significant difference between groups.

IMPATTO DEL BMI SULLA RISPOSTA AGLI ANTI-TNF

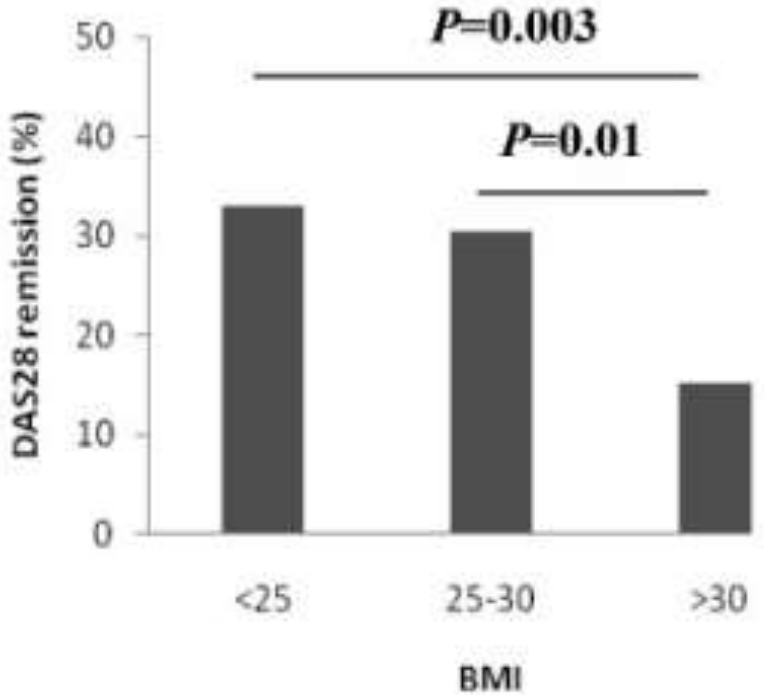


Figure 1. Percentage of Disease Activity Score in 28 joints (DAS28) remission at the 12th month of anti–tumor necrosis factor α therapy in rheumatoid arthritis patients according to body mass index (BMI) categories.

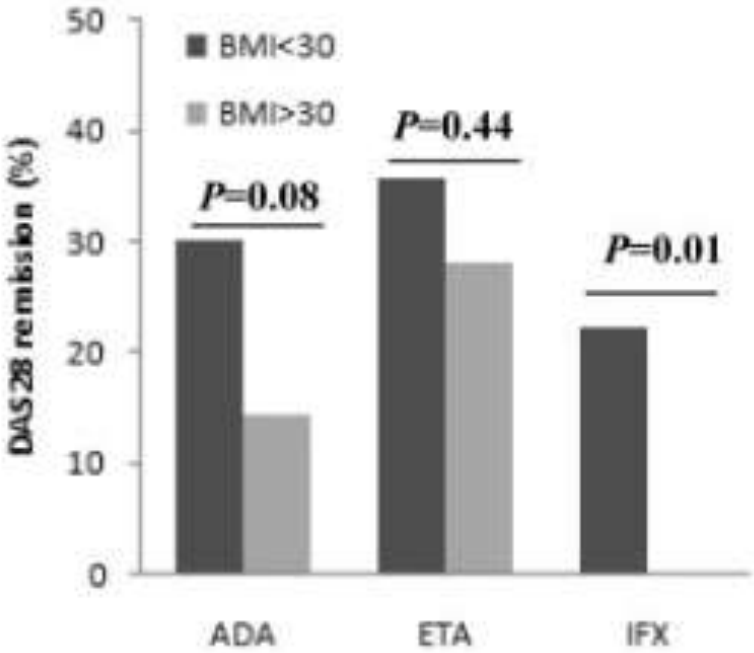


Figure 2. Percentage of Disease Activity Score in 28 joints (DAS28) remission in obese and nonobese rheumatoid arthritis patients treated with adalimumab (ADA), etanercept (ETA), and infliximab (IFX). None of the obese patients responded to IFX. BMI = body mass index.

Aliment Pharmacol Ther. 2017;46:883–891.

J Am Acad Dermatol. 2019 Aug 7. pii: S0190-9622(19)32498-3. doi: 10.1016/j.jaad.2019.07.103.

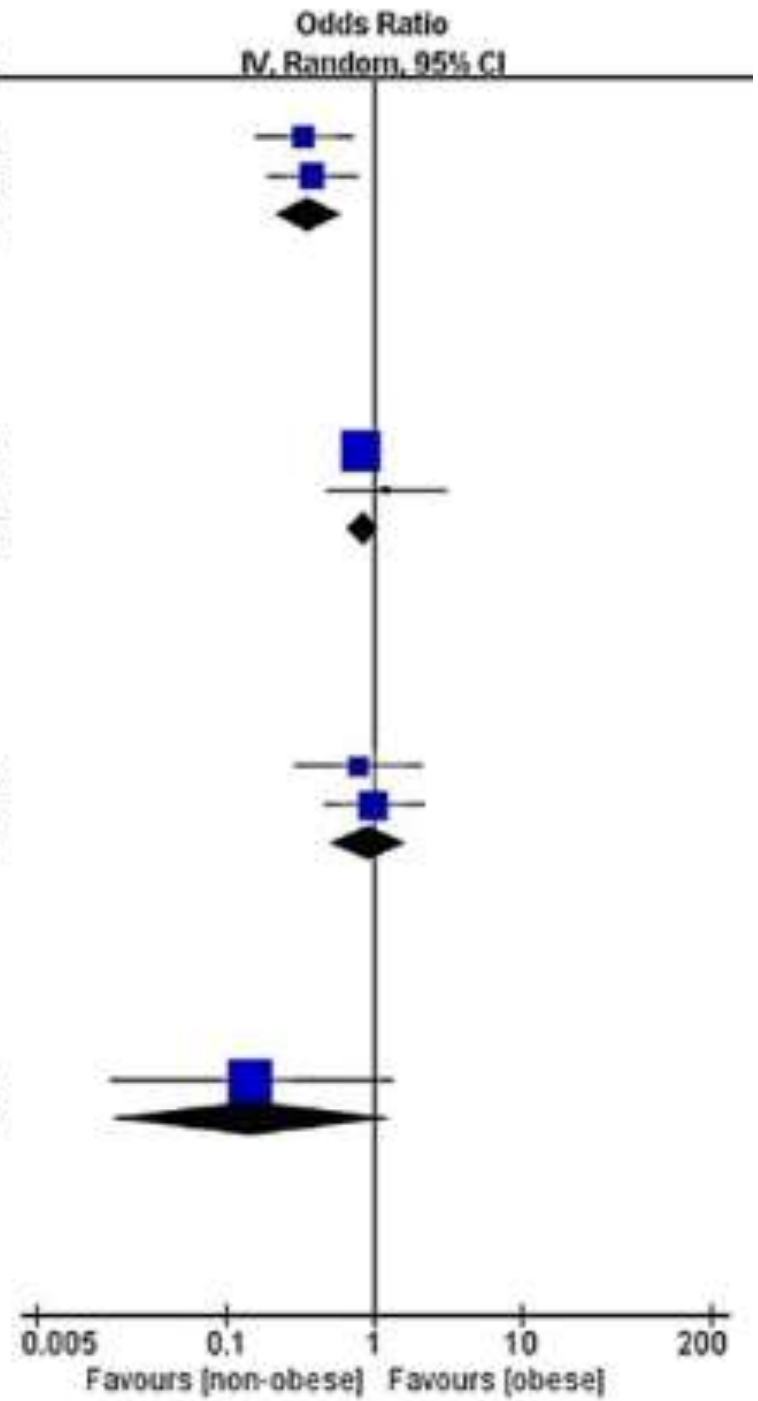
J Dermatol. 2018 Sep;45(9):1130-1134. doi: 10.1111/1346-8138.14526.

Clin Rheumatol. 2017 Dec;36(12):2655-2665. doi: 10.1007/s10067-017-3788-1.

Arthritis Care Res (Hoboken). 2013 Jan;65(1):94-100. doi: 10.1002/acr.21768.

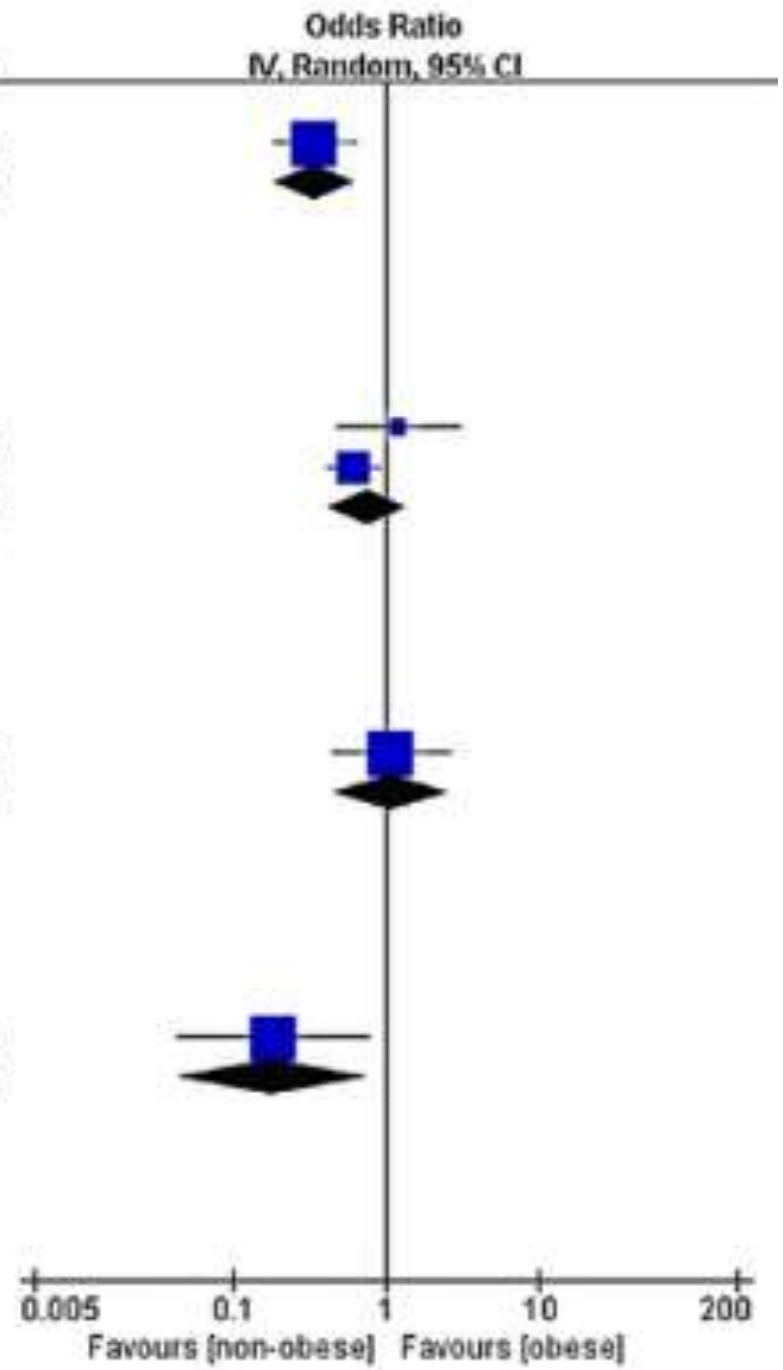
a

Study or Subgroup	obese Events	Total	non-obese Events	Total	Weight	Odds Ratio IV, Random, 95% CI
1.1.1 Anti-TNF agents						
Iannone 2015	11	66	44	117	46.4%	0.33 [0.16, 0.70]
Gremese 2013	10	66	184	575	53.6%	0.38 [0.19, 0.76]
Subtotal (95% CI)		**132**		**692**	**100.0%**	**0.36 [0.21, 0.59]**
Total events	21		228			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 3.97 (P < 0.0001)						
1.1.2 Abatacept						
D'Agostino 2017	95	433	262	1023	92.3%	0.82 [0.62, 1.07]
Gardette 2016	8	39	18	102	7.7%	1.20 [0.48, 3.05]
Subtotal (95% CI)		**472**		**1125**	**100.0%**	**0.84 [0.65, 1.09]**
Total events	103		280			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.32 (P = 0.19)						
1.1.3 Tocilizumab						
Gardette 2016	7	25	30	90	38.2%	0.78 [0.29, 2.07]
Pers 2015	13	32	71	175	61.8%	1.00 [0.47, 2.16]
Subtotal (95% CI)		**57**		**265**	**100.0%**	**0.91 [0.50, 1.66]**
Total events	20		101			
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.76)						
1.1.4 Rituximab						
Iannone 2015	1	15	8	24	100.0%	0.14 [0.02, 1.29]
Subtotal (95% CI)		**15**		**24**	**100.0%**	**0.14 [0.02, 1.29]**
Total events	1		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.73 (P = 0.08)						



b

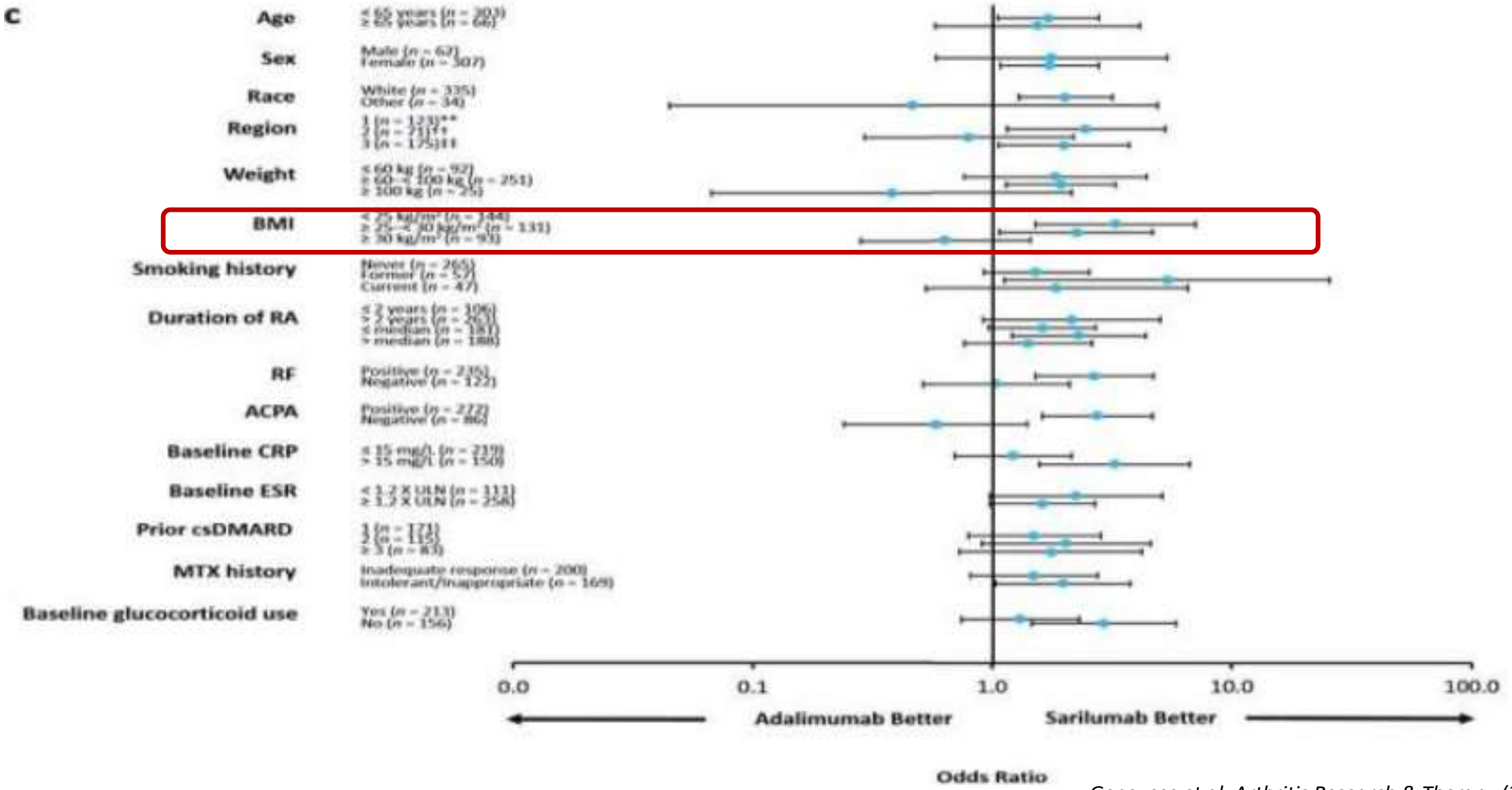
Study or Subgroup	obese Events	Total	non-obese Events	Total	Weight	Odds Ratio IV, Random, 95% CI
1.2.1 Anti-TNF agents						
Iannone 2015	28	66	80	117	100.0%	0.34 [0.18, 0.64]
Subtotal (95% CI)		**66**		**117**	**100.0%**	**0.34 [0.18, 0.64]**
Total events	28		80			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.38 (P = 0.0007)						
1.2.2 Abatacept						
Gardette 2016	8	39	18	102	29.2%	1.20 [0.48, 3.05]
Mariettea 2017	41	155	179	488	70.8%	0.62 [0.42, 0.93]
Subtotal (95% CI)		**194**		**590**	**100.0%**	**0.75 [0.42, 1.36]**
Total events	49		197			
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 1.65$, df = 1 (P = 0.20); $I^2 = 39\%$						
Test for overall effect: Z = 0.94 (P = 0.35)						
1.2.3 Tocilizumab						
Gardette 2016	11	25	38	90	100.0%	1.08 [0.44, 2.63]
Subtotal (95% CI)		**25**		**90**	**100.0%**	**1.08 [0.44, 2.63]**
Total events	11		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.87)						
1.2.4 Rituximab						
Iannone 2015	4	15	16	24	100.0%	0.18 [0.04, 0.76]
Subtotal (95% CI)		**15**		**24**	**100.0%**	**0.18 [0.04, 0.76]**
Total events	4		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.35 (P = 0.02)						



BMI, Ab and SARILUMAB

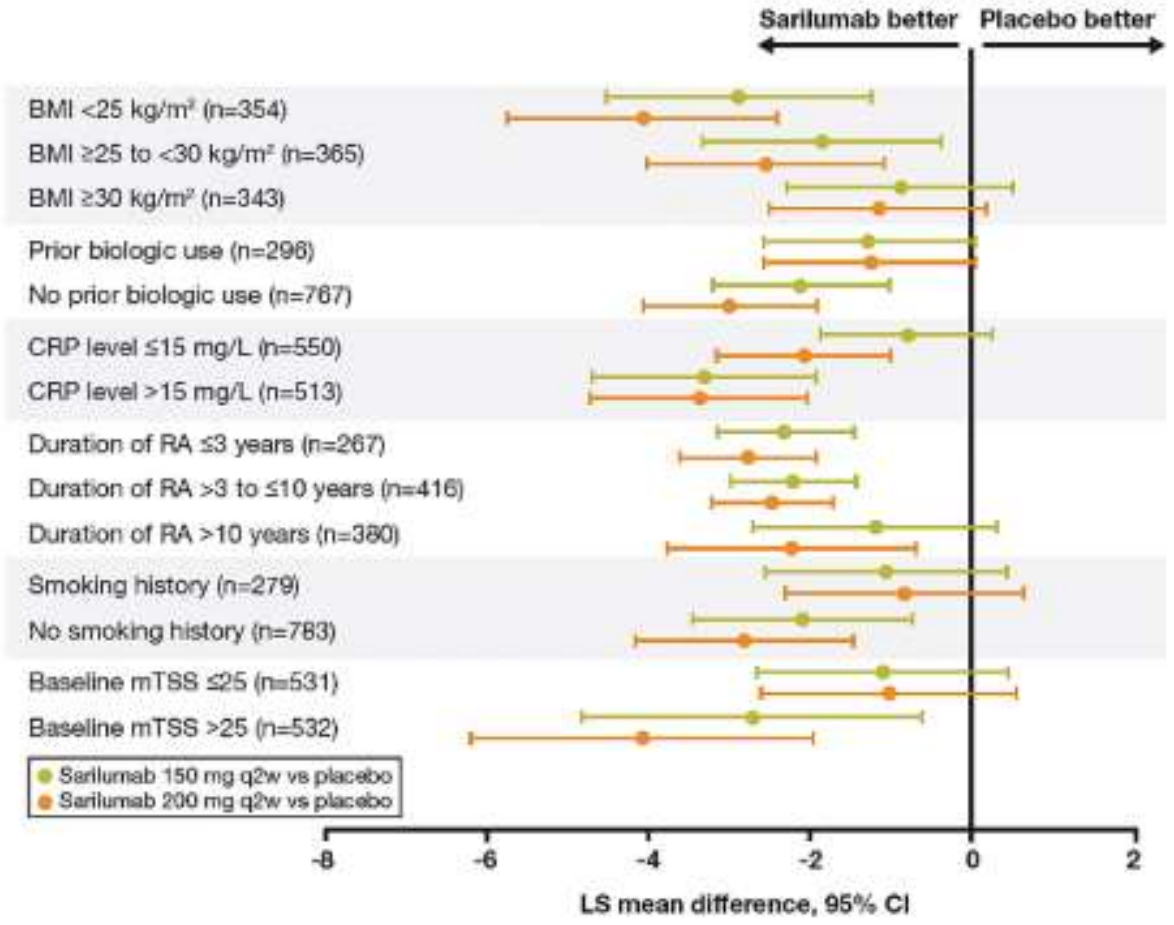
Odds ratio (95% CI) for ACR20 response by subpopulation at week 24.

Sarilumab 200 mg q2w vs. adalimumab 40mg q2w in MTX-IR/INT patients.



Genovese et al. Arthritis Research & Therapy (2020) 22:139

BMI and SARILUMAB



Genovese et al. Arthritis Research & Therapy (2020) 22:139

JAK-i

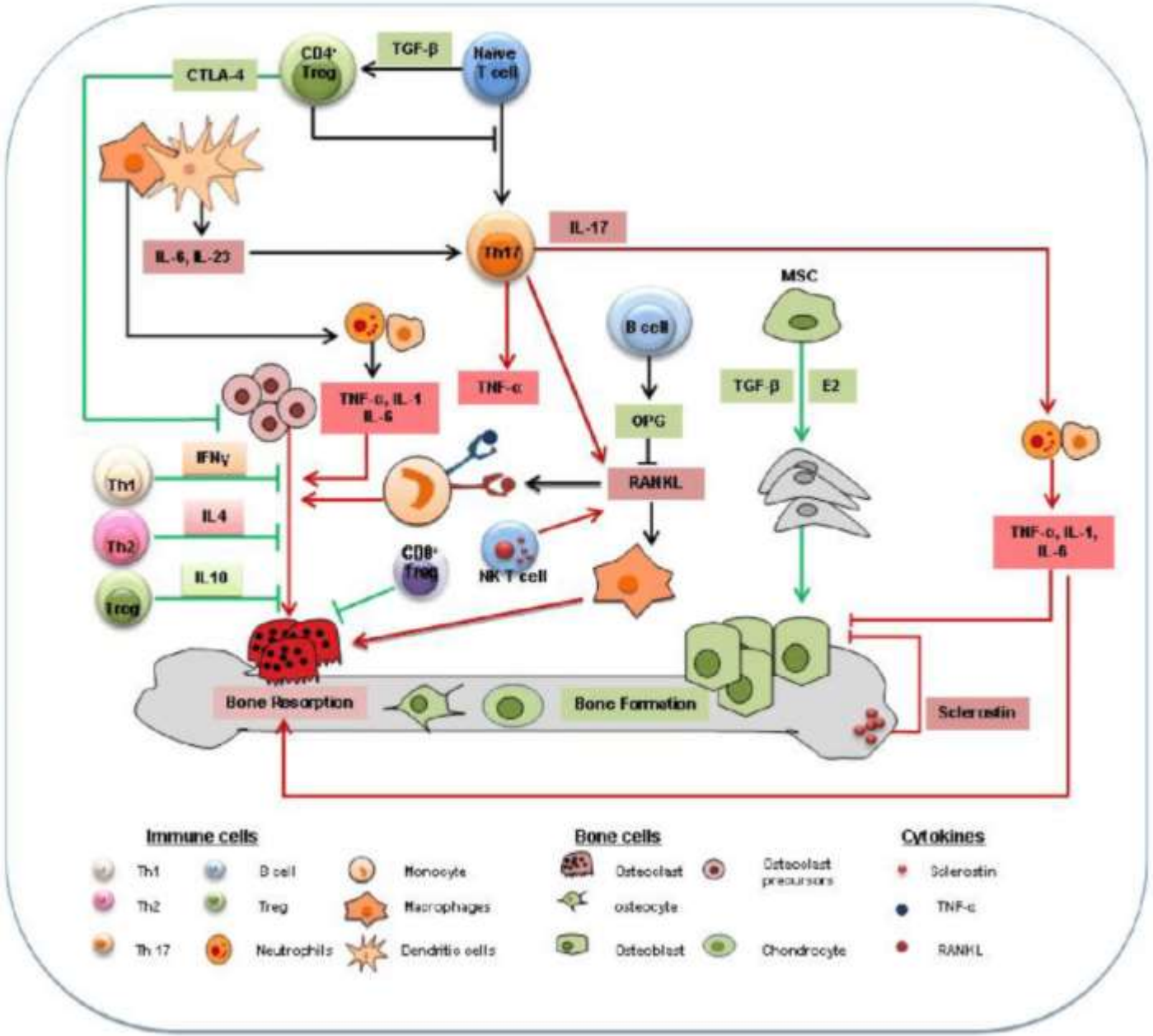
DAS28 score <2.6, were 11% for obese patients, 24% for overweight patients, and 20% for normal weight patients. The regression model indicated a significant negative effect of obesity on low disease activity achievement compared with normal weight.

Neither the dosage of JAK inhibitors nor combination/mono-therapy had an effect on treatment response.

Obesity but not overweight had a negative impact on the achievement of LDA in RA patients treated with JAKi.

ACR/ARHP 2018.

BONE LOSS THROUGH OSTEO-IMMUNE NETWORK



- Th1 e Th2 secernono IFN-γ e IL-4 rispettivamente portando all'inibizione dell'osteoclastogenesi.
- Treg → IL-10, CTLA4 (che può legarsi a CD80 / CD86 sui precursori degli osteoclasti) che promuovono l'apoptosi e l'inibizione del riassorbimento osseo**.**
- **Th17 →citochine osteoclastogeniche (IL-1, IL-6, IL-17, TNF-α), portando così a una maggiore osteoclastogenesi e perdita ossea.**
- I linfociti B producono OPG che blocca l'espressione di RANKL
- Macrofagi, DC e monociti secernono TNF-α, IL-1 e IL-6 → osteoclastogenesi

Hamid Y Dar et al, Front Biosci (Landmark Ed) 2018

TNF-α

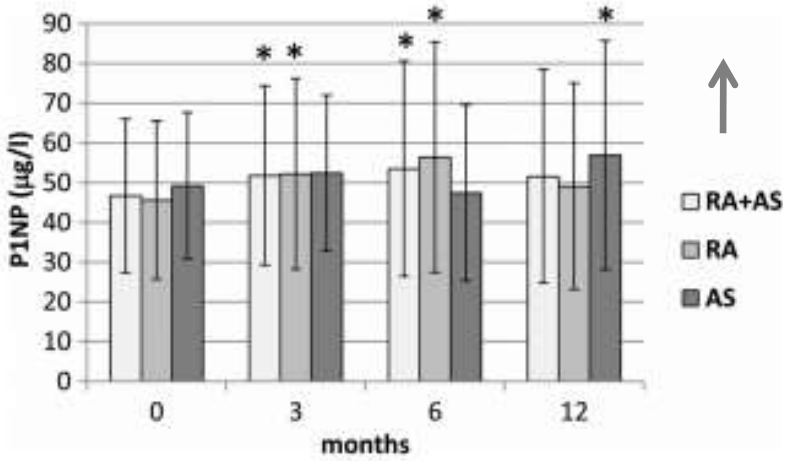
- ↑ differenziazione OC tramite attivazione di NFκβ pathway da parte di RANK/RANKL
- ↑ l'espressione di M-CSF e RANKL in diverse cellule bersaglio, inclusi gli OB, cellule T e B, promuovendo indirettamente la differenziazione degli OC
- ↑ Apoptosi OB
- ↓ differenziazione e attivazione OB tramite NFκβ pathway
- 🚫 apoptosi degli osteoclasti attraverso la chinasi mTOR / S6
- sovraregolazione degli inibitori della proteina 1 (DKK1) e della sclerostina con conseguente inibizione della via della Wnt/β-catenina

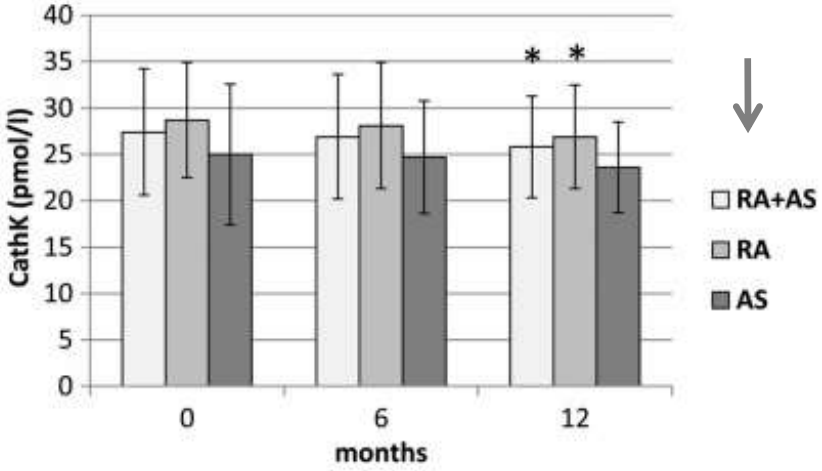
Vivian K. Kawai et al, 2012

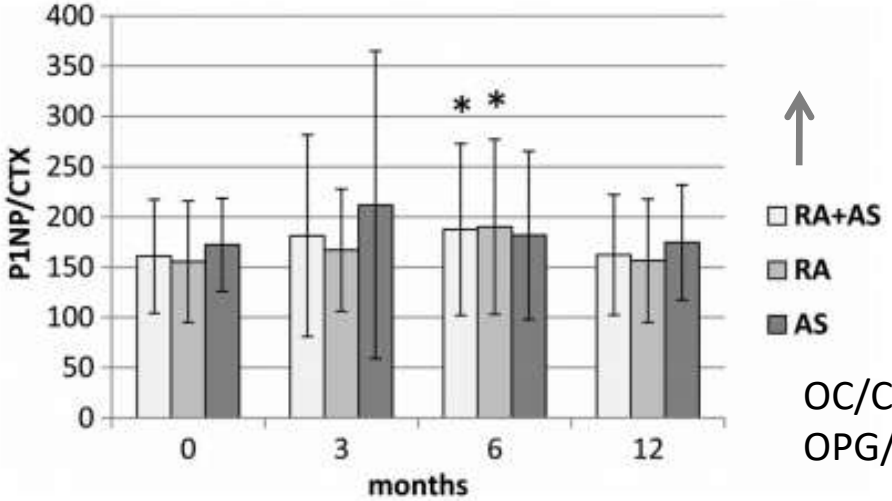
Clinical Rheumatology (2020) 39:167–175
https://doi.org/10.1007/s10067-019-04771-3

ORIGINAL ARTICLE

Effects of 1-year anti-TNF-α therapies on bone mineral density and bone biomarkers in rheumatoid arthritis and ankylosing spondylitis

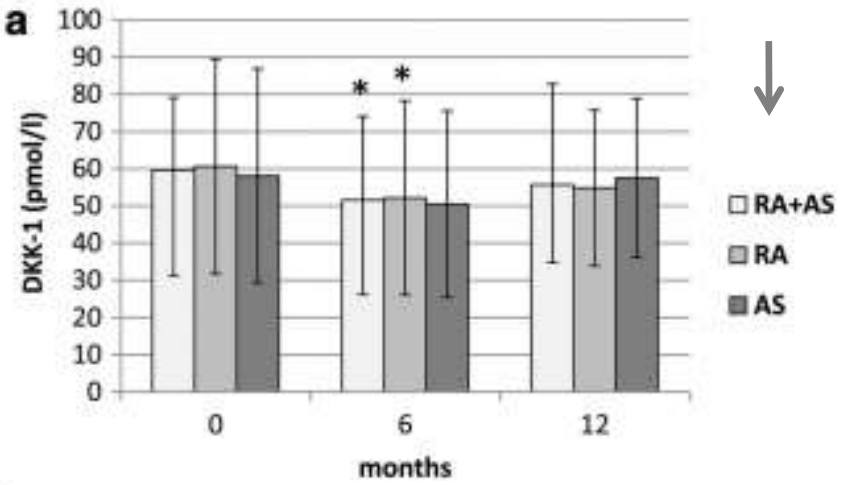


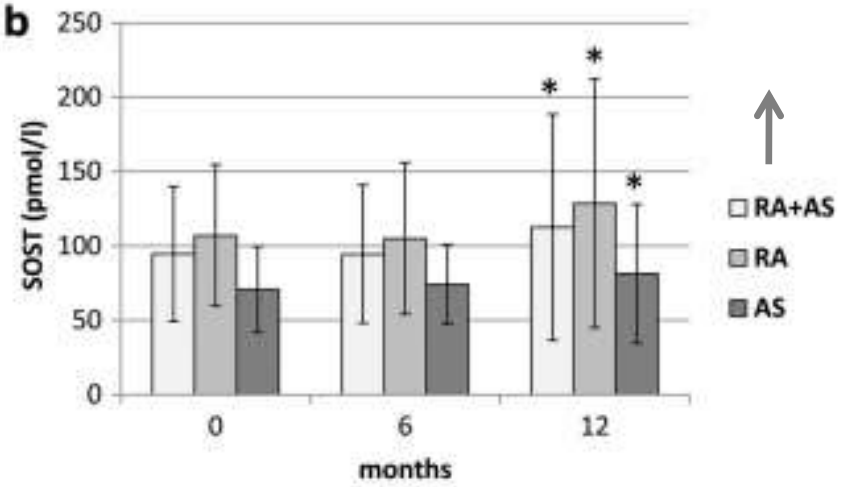




P1NP procollagen type I N-propeptid
CathK cathepsin K
CTX C-terminal telopeptide
DKK-1 Dickkopf-1
SOST sclerostin
PTH parathyroid hormone

OC/CTX
OPG/RANK-L
} No relevant change





With respect to the RANKL pathway, in the full cohort or in RA or AS patients, sRANKL and OPG levels did not show any differences during anti-TNF therapy. In addition, Ca, P, vitamin D3 and PTH levels also did not change during the 1-year period (data not shown).

K. Gulyàs et al. 2019

Curr Opin Rheumatol. 2012 September ; 24(5): 576–585. doi:10.1097/BOR.0b013e328356d212.

Effects of Anti-Tumor Necrosis Factor α (anti-TNF) agents on Bone

Table 3 Median (IQR) BMD change in the hands, hip and spine, in percentages of baseline, in the four treatment groups after 1 and 2 years of follow-up

BeSt →

	Sequential monotherapy (group 1)	Step-up combination therapy (group 2)	Initial combination with prednisone (group 3)	Initial combination with infliximab (group 4)
BMD loss in hands				
After 1 year	−2.6 (−5.4 to −0.8)	−1.7 (−5.1 to −0.1)	−0.6 (−2.2 to 0.3)	−0.9 (−2.8 to 0.5)
After 2 years	−3.6 (−6.8 to −1.4)	−3.3 (−6.8 to −0.2)	−1.4 (−5.4 to −0.1)	−1.6 (−4.7 to 0.3)
BMD loss in hip				
After 1 year	−1.6 (−3.5 to 1.1)	−0.4 (−2.7 to 2.3)	−1.0 (−4.6 to 1.7)	−0.6 (−2.7 to 2.1)
After 2 years	−1.1 (−2.9 to 2.0)	−0.2 (−2.6 to 2.3)	−0.2 (−2.6 to 3.2)	−0.6 (−3.3 to 2.0)
BMD loss in spine				
After 1 year	−0.2 (−2.8 to 2.0)	−1.1 (−2.5 to 1.4)	−1.0 (−2.7 to 1.8)	−0.1 (−3.1 to 1.1)
After 2 years	−0.4 (−4.6 to 2.6)	−1.6 (−4.6 to 1.1)	−0.5 (−3.9 to 2.1)	−1.0 (−3.3 to 1.4)

BMD, bone mineral density.

Table 5 Demographic and disease related factors associated with BMD loss after 1 year in the hands, hip and spine derived by multivariate analyses

	BMD loss in hands		BMD loss in hip		BMD loss in spine	
Variable	β coefficient	p Value	β coefficient	p Value	β coefficient	p Value
Postmenopausal status	−3.17	0.000	–	–	–	–
CRP at baseline	−0.025	0.000	–	–	–	–
ΔErosions 0–1	−0.12	0.021	−0.19	0.004	–	–
BP use 0–1	–	–	2.50	0.011	4.02	0.000

BMD, bone mineral density; BP, bisphosphonates; CRP, C-reactive protein.
Data are adjusted for the significant associations derived from the univariate analyses and randomisation between the four treatment groups.

- Tp convenzionale ↑ perdita ossea mani vs gruppo 4

- Questa differenza è rimasta significativa dopo aggiustamento per antiriassorbitivi, ma è scomparsa quando nell'analisi è stato incluso il cambiamento nell'attività della malattia.

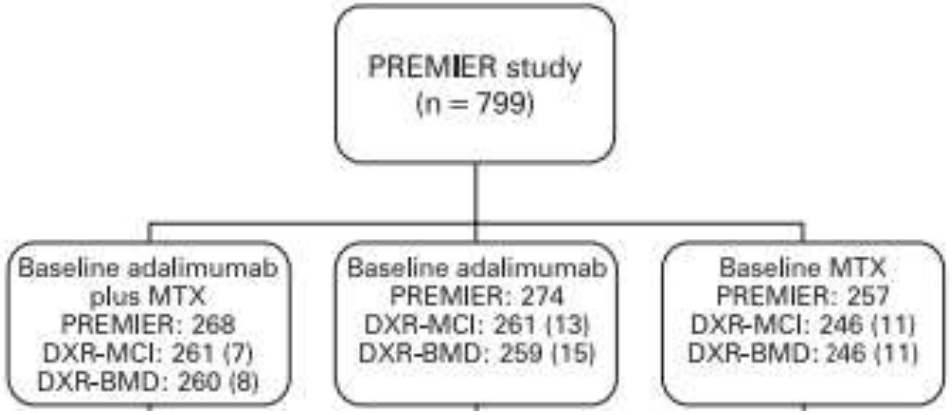
- Progressione radiografica, postmenopausa e infiammazione erano associati alla perdita ossea della mano dopo l'aggiustamento per varie covariate

- Post-hoc in base alla risposta tp: ↑ dell'osso MTC correlato a remissione clinica, indipendentemente dall'uso precedente o corrente della terapia anti-TNF

Vivian K. Kawai et al, 2012
M Gu¨ler-Yu¨kse et al Ann Rheum Dis, 2007

Curr Opin Rheumatol. 2012 September ; 24(5): 576–585. doi:10.1097/BOR.0b013e328356d212.

Effects of Anti-Tumor Necrosis Factor α (anti-TNF) agents on Bone



- MTX+ADA minore perdita ossea della mano vs ADA e MTX in monoterapia
- Perdita ossea correlata con mancato utilizzo di adalimumab, età, infiammazione
- MTX mono: ↑ perdita se PCR e/o DAS28 ↑
- MTX+ADA ↓ ossea indipendente dall'attività di malattia o PCR
- possibile effetto diretto del TNFα sull'attivazione degli osteoclasti

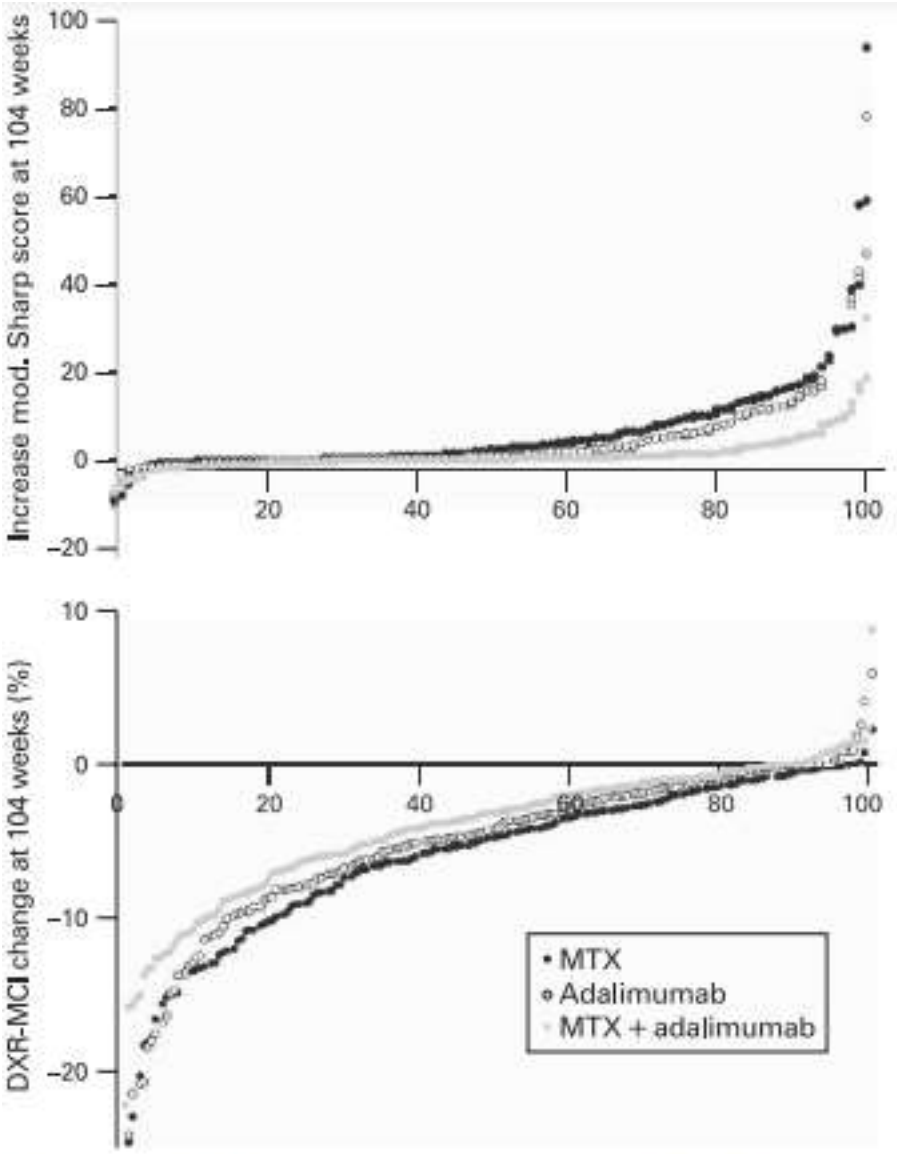


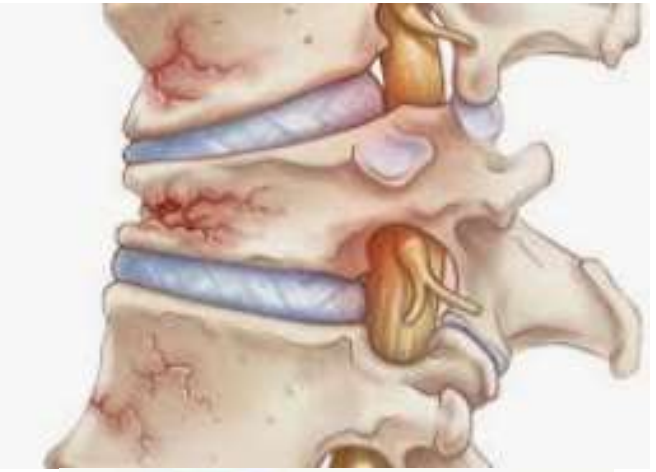
Figure 3 Cumulative probability plot: changes in DXR–MCI and radiographic scores at 104 weeks in PREMIER. DXR, digital *x* ray radiogrammetry; MCI, metacarpal cortical index; mod Sharp score, modified total Sharp score; MTX, methotrexate.

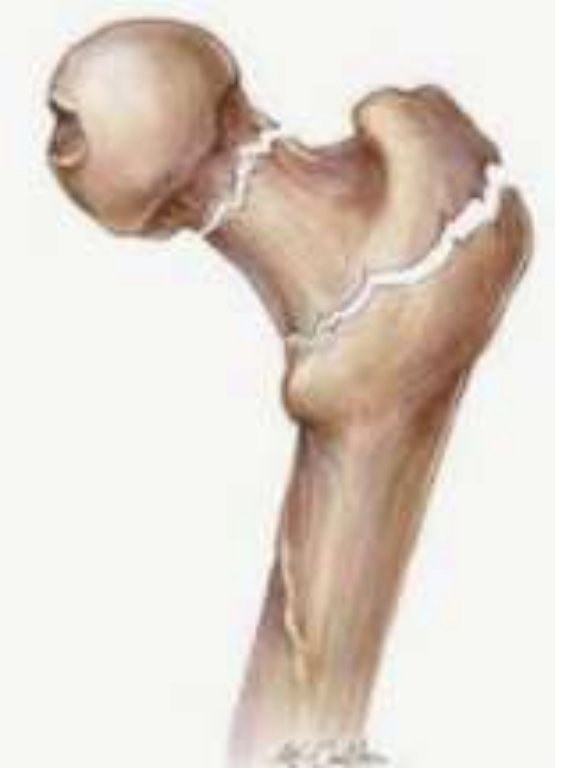
Vivian K. Kawai et al, 2012
M Hoff et al, *Ann Rheum Dis 2009*

Curr Opin Rheumatol. 2012 September ; 24(5): 576–585. doi:10.1097/BOR.0b013e328356d212.

Effects of Anti-Tumor Necrosis Factor α (anti-TNF) agents on Bone

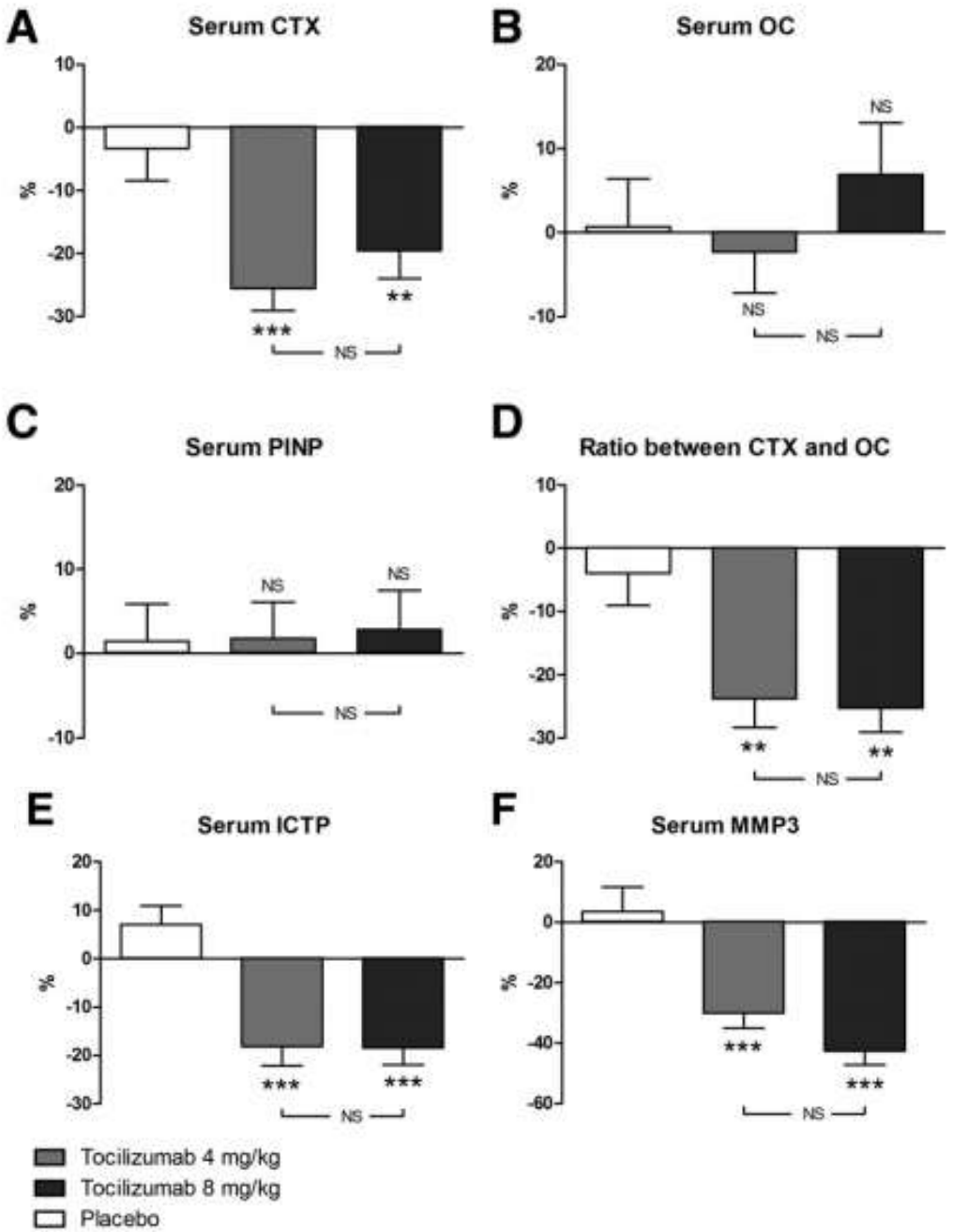
- Dati contrastanti
- Arresto perdita ossea colonna e femore
- BMD ↓ nei controlli storici che hanno ricevuto solo MTX, conservati nei pazienti IFX+MTX, correlata a risposta al trattamento
- BMD ↓ MTX+pcb vs MTX+IFX, ma correlato a PCR e danno radiografico
- BeSt: ↓ BMD inferiore se concomitanti bifosfonati (no correlazione con tp anti-RA)





Vivian K. Kawai et al, 2012
Marotte H et al Arthritis Res Ther. 2007
Haugeberg G e al Ann Rheum Dis 2009

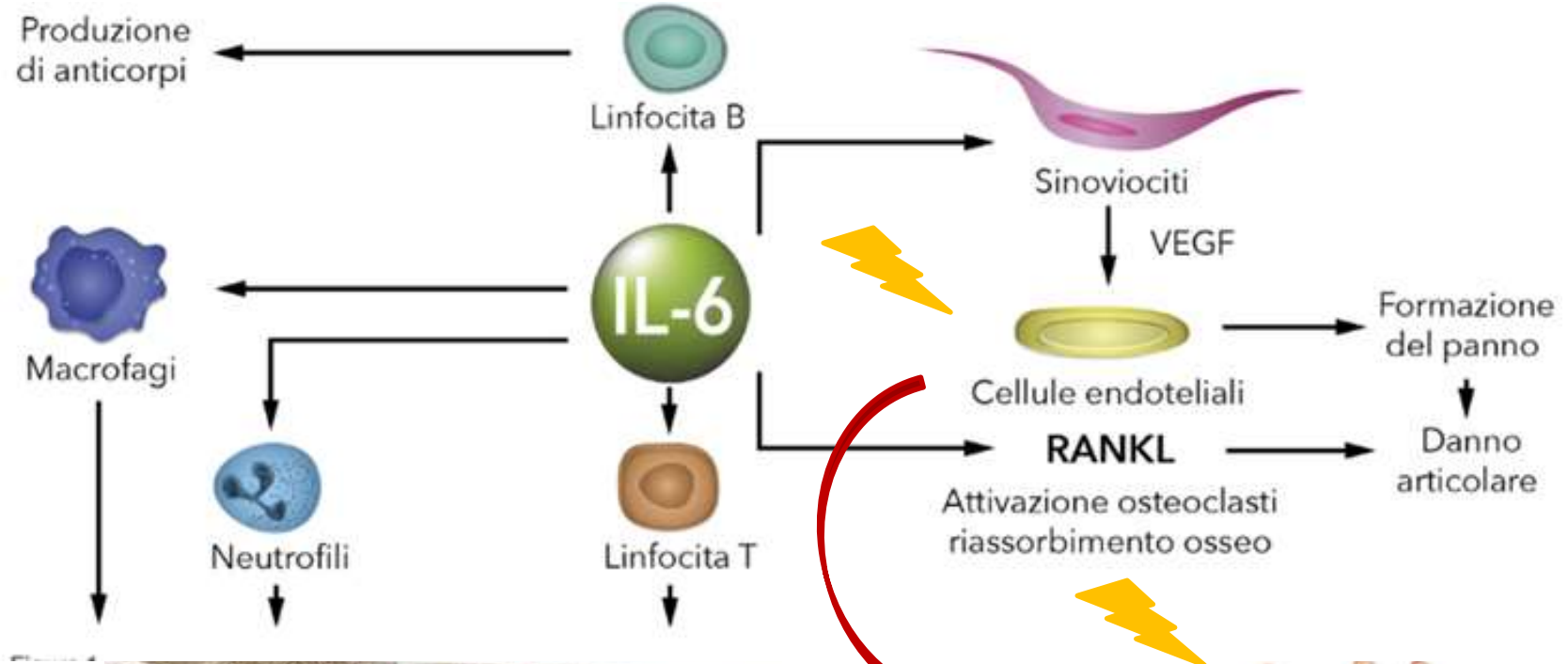
IL-6 ANTAGONIST AND BONE LOSS

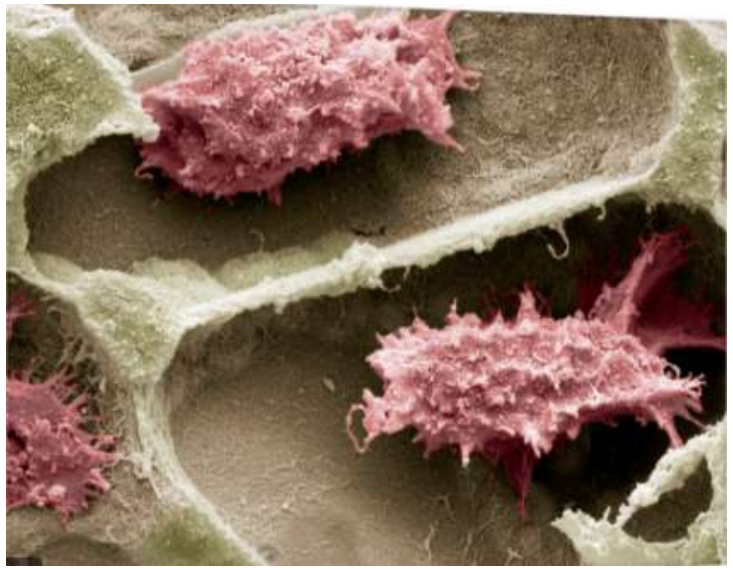


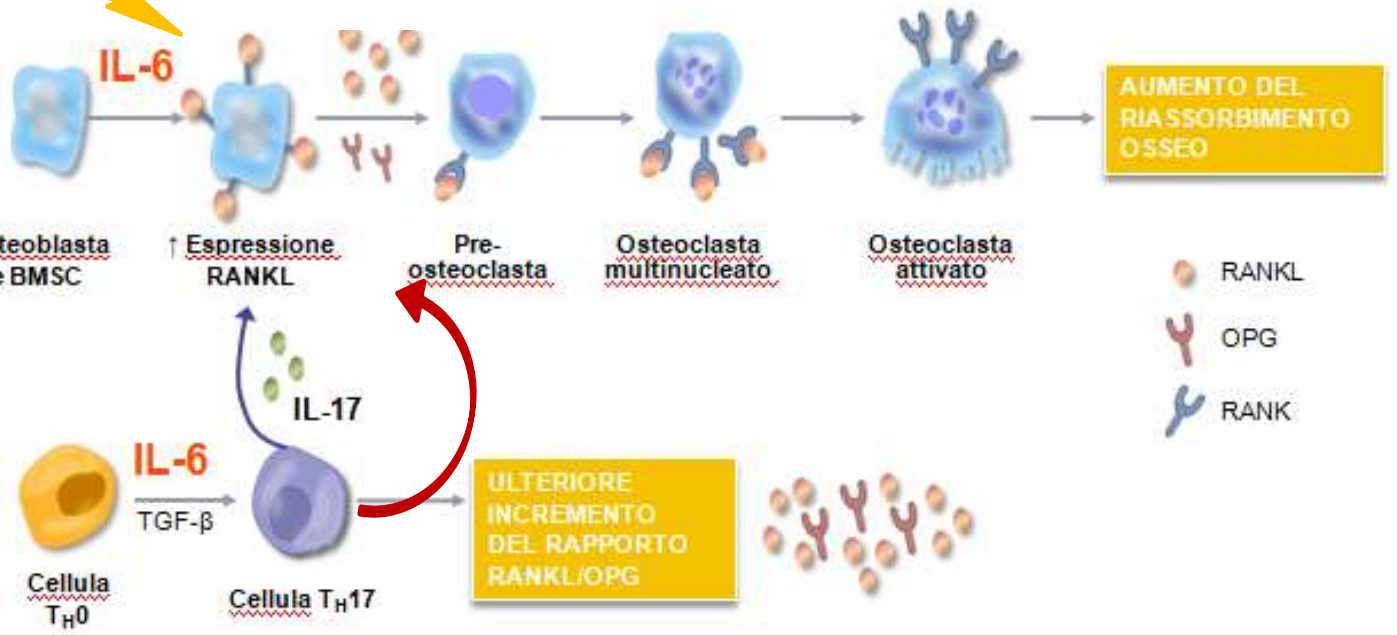
- Stretta correlazione con flogosi
- IL-6/PCR
- Limite: biomarkers vs BMD

Morten A. Karsdal et al, Semin Arthritis Rheum 2012

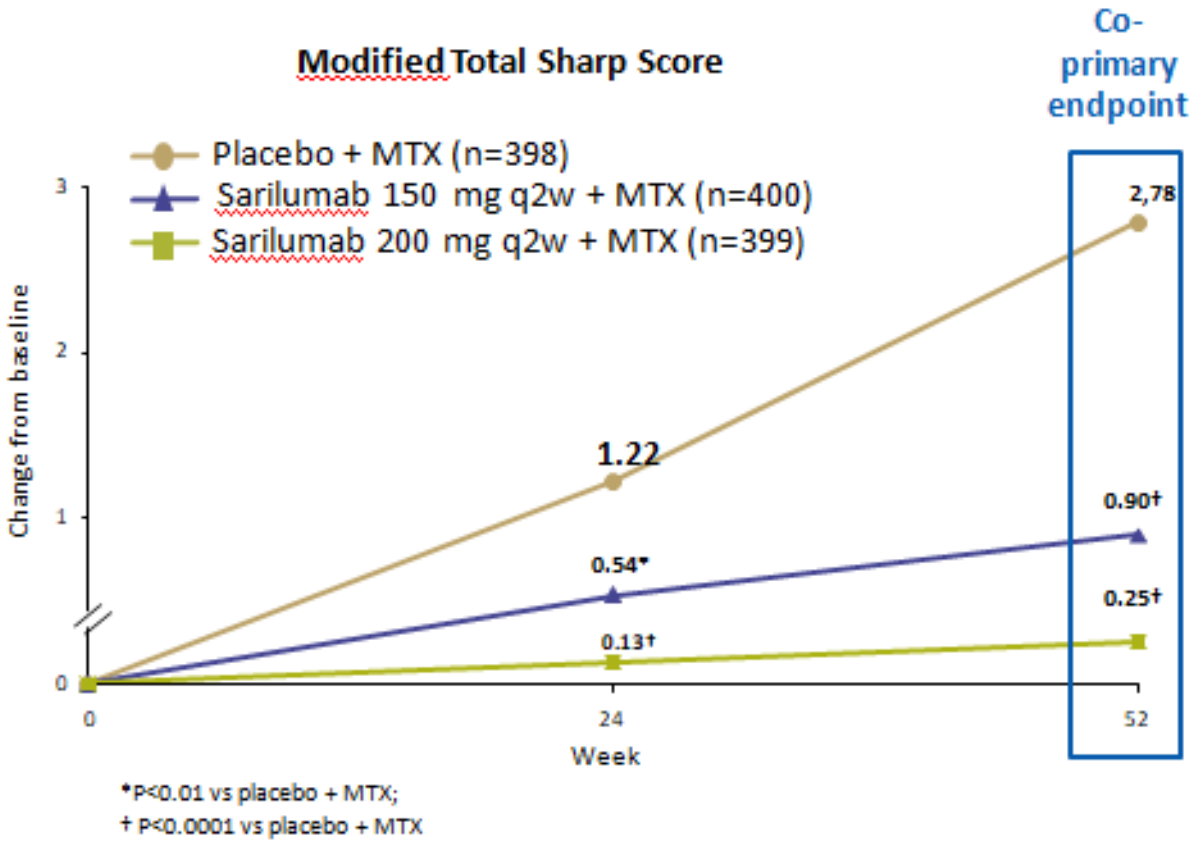
IL-6 : EFFECT ON BONE METABOLISM







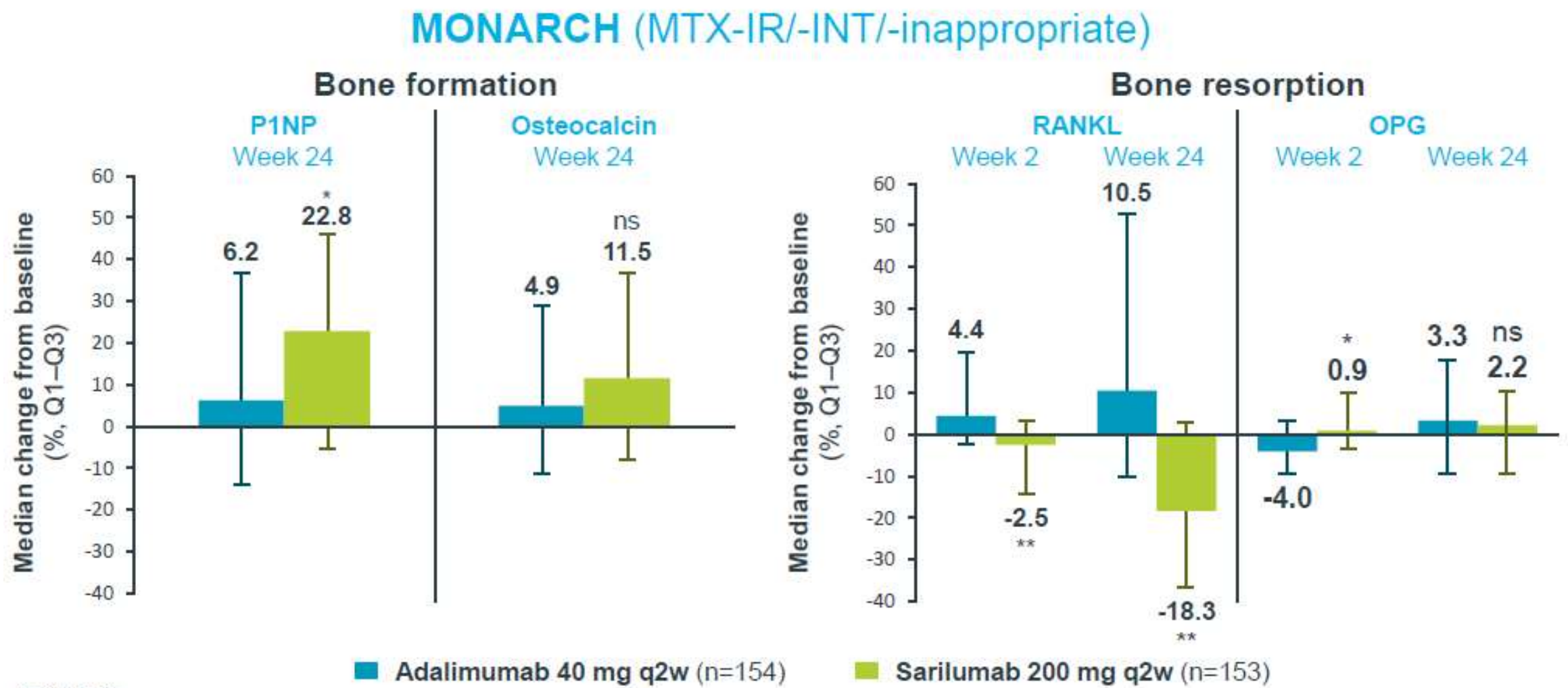
IL-6 INHIBITORS: EFFECT ON BONE METABOLISM



n (%)	Placebo + MTX (n=398)	Sarilumab 150 mg q2w + MTX (n=400)	Sarilumab 200 mg q2w + MTX (n=399)
Week 24			
No progression	158 (39.7%)	185 (46.3%)	226 (56.6%)
P-value vs placebo†	–	NS	<0.0001
Week 52			
No progression	154 (38.7%)	191 (47.8%)	222 (55.6%)
P-value vs placebo*	–	0.0094	<0.0001

91%

SARILUMAB vs ADALIMUMAB on bone resorption



INT, intolerant

*Adjusted p<0.05 versus adalimumab; **Adjusted p<0.01 versus adalimumab (Benjamini–Hochberg procedure)

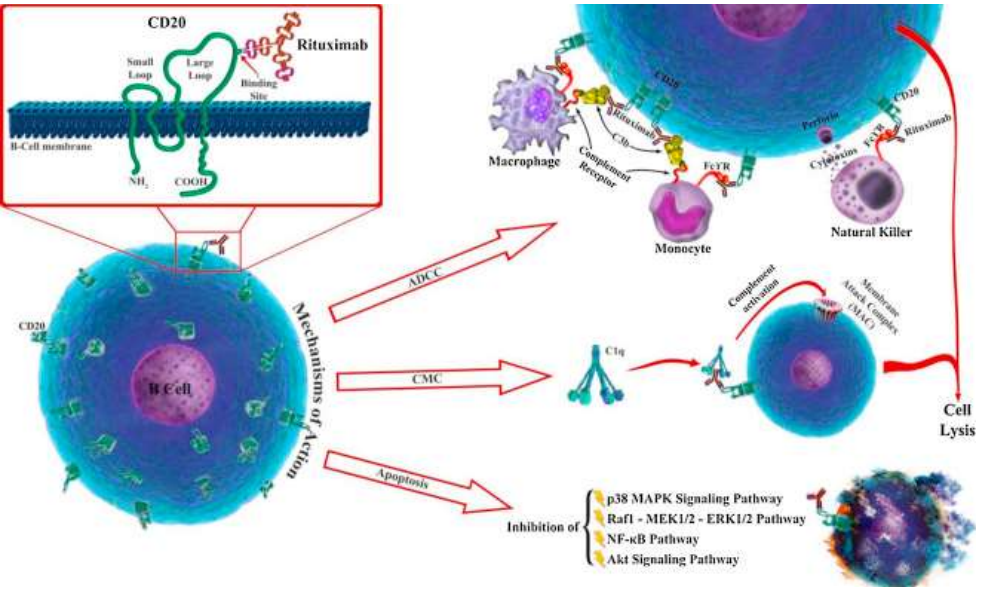
a. Numeric differences only for osteocalcin.

Gabay C, et al. *Ann Rheum Dis* 2017;76(Suppl. 2):570

Gabay et al. Arthritis Research & Therapy (2020) 22:70

Rheumatol Int (2011) 31:269–272

Influence of Rituximab on markers of bone remodeling in patients with rheumatoid arthritis: a prospective open-label pilot study



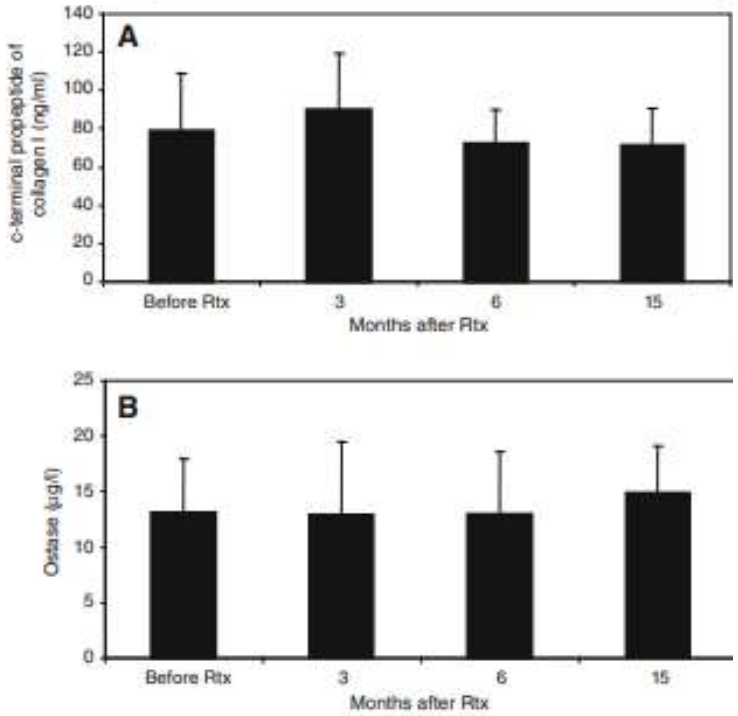


Fig. 1 Bone formation markers

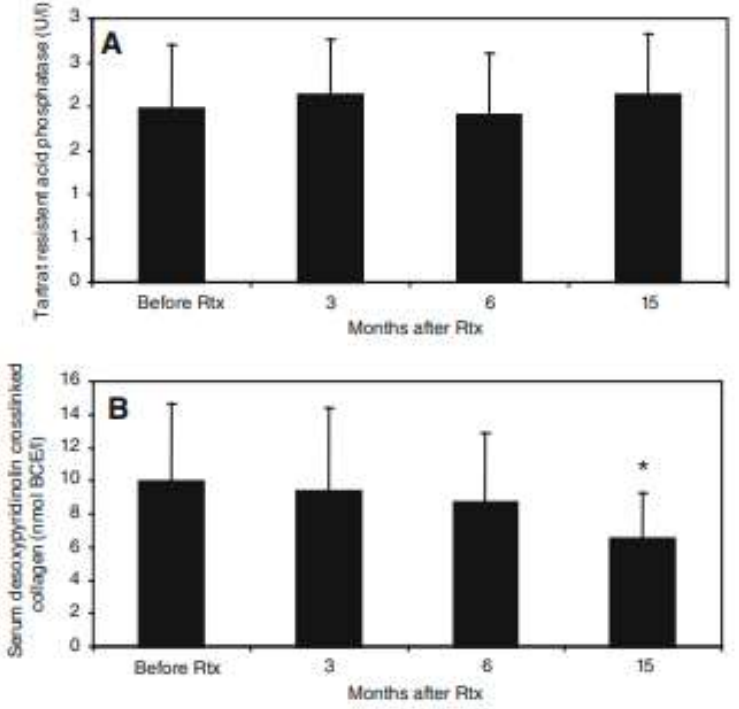


Fig. 2 Bone resorption markers (* $P < 0.001$ vs. patients before Rtx)

Osteoporos Int (2011) 22:3067–3072

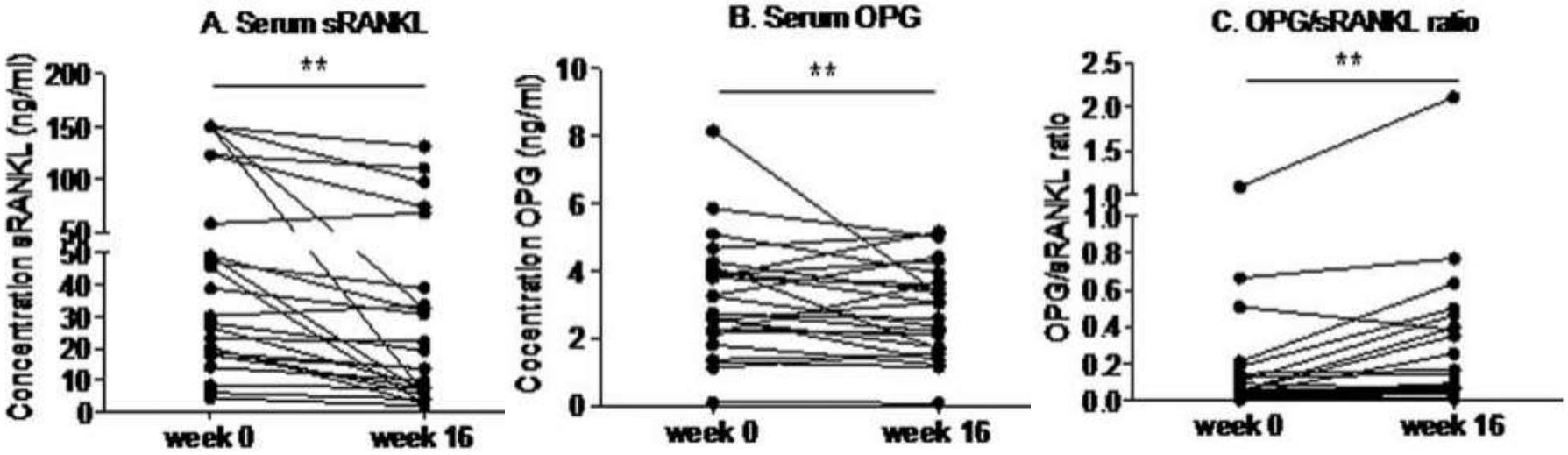
Suppression of bone turnover by B-cell depletion in patients with rheumatoid arthritis

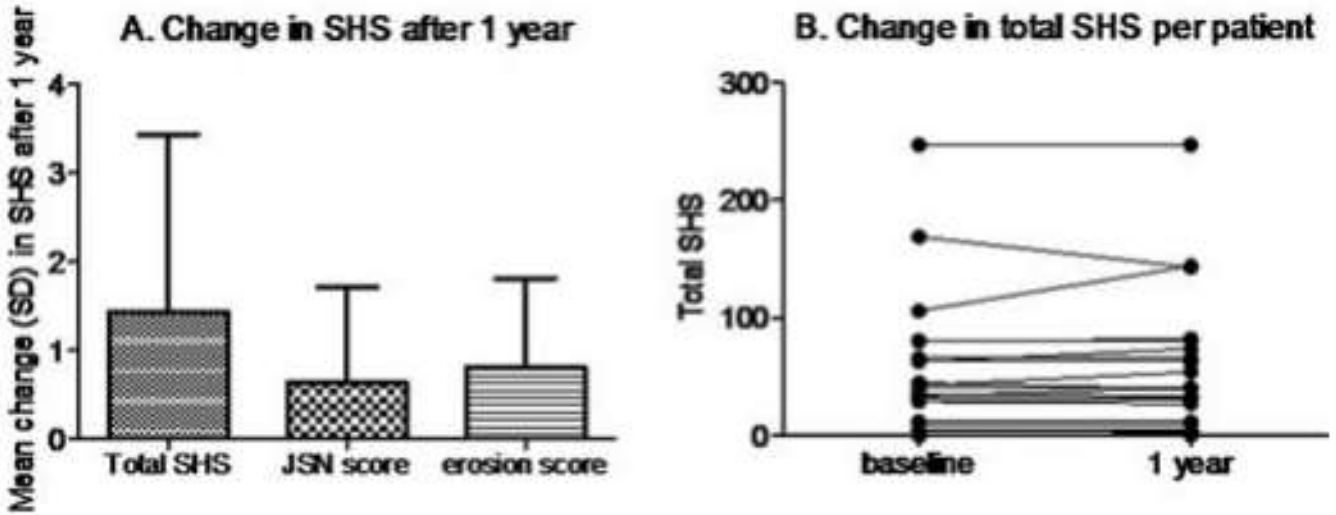
- Significativa ↓ del riassorbimento osseo dopo 6 mesi da RTX (βCTX), concomitante a ↓DAS28.
- ↑ significativo del P1NP
- Nessuna variazione significativa nei livelli di osteocalcina o OPG.
- Variazione % vs basale di βCTX in un sottogruppo di pazienti (non trattati con prednisolone o bisfosfonato) erano significativamente correlati con la riduzione % del DAS28

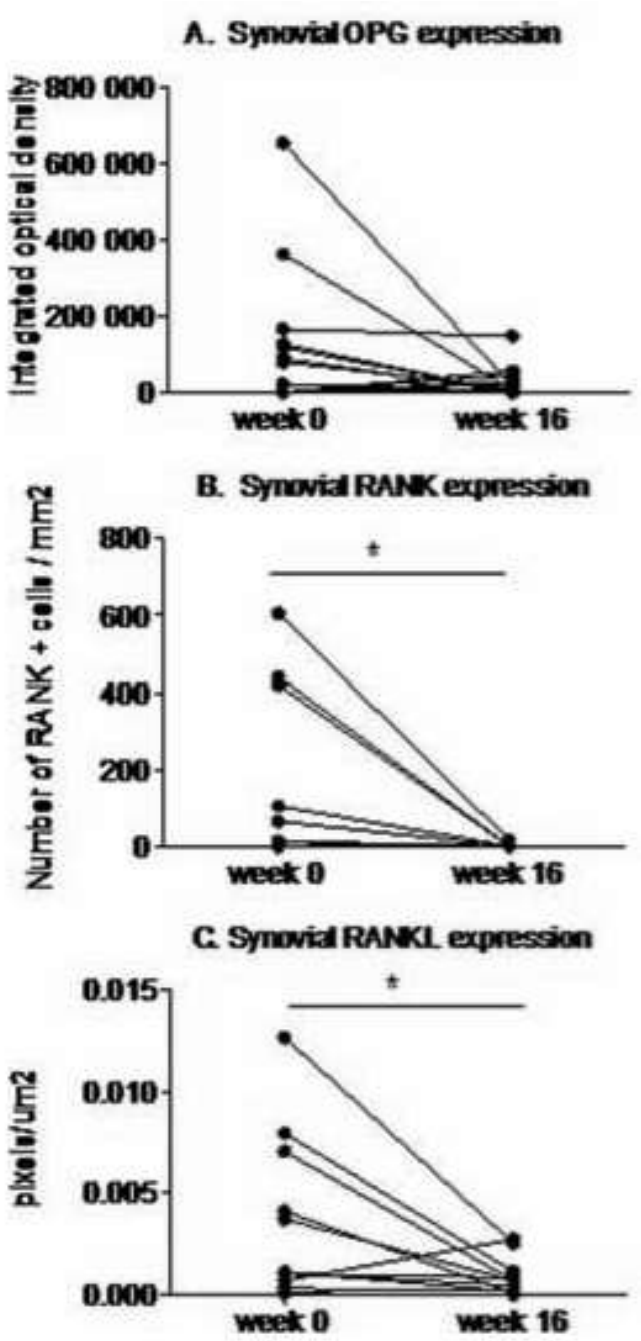
Gert Hein et al, 2011; G. Wheater et al, 2011;

Ann Rheum Dis. 2012 Jan;

Rituximab abrogates joint destruction in rheumatoid arthritis by inhibiting osteoclastogenesis





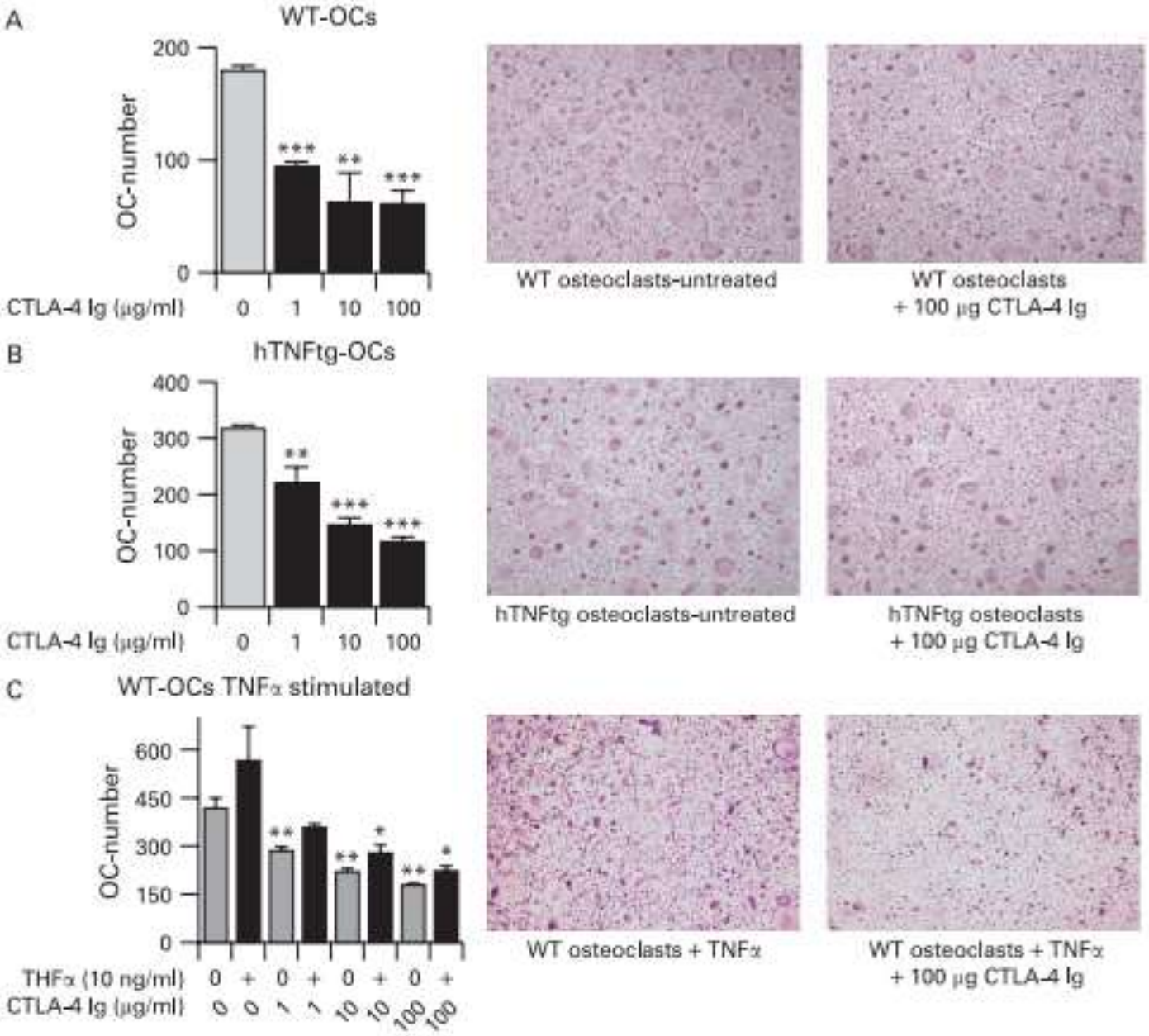


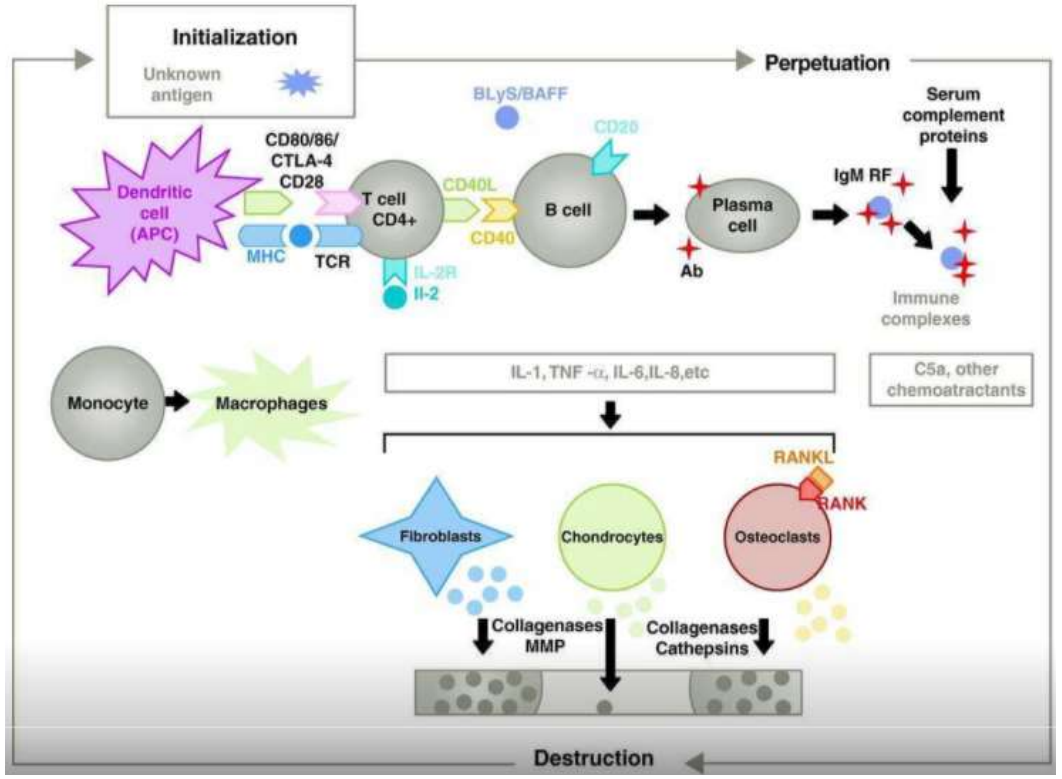
Il trattamento con RTX è associato a una diminuzione dei precursori degli OC sinoviali e dell'espressione di RANKL e ad un aumento del rapporto OPG/RANKL nel siero.

Maria J H Boumans et al, 2012

Ann Rheum Dis 2008;67:1603–1609.

CTLA-4 directly inhibits osteoclast formation





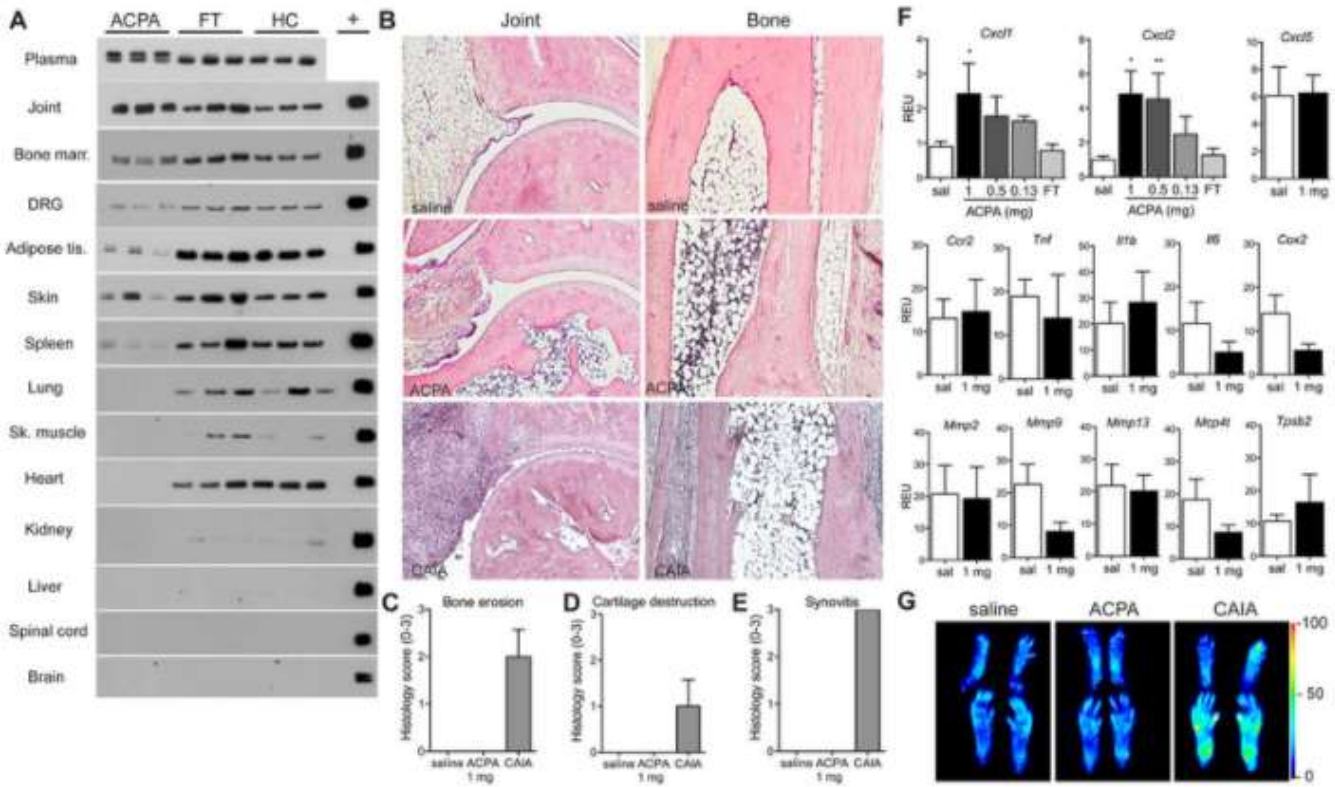
Coltura con: 30 ng/ml di fattore stimolante le colonie di macrofagi (MCSF) e 50 ng/ml di RANKL per 6 giorni.
Varie dosi di CTLA-4 sono state aggiunte nei giorni 2 e 5.

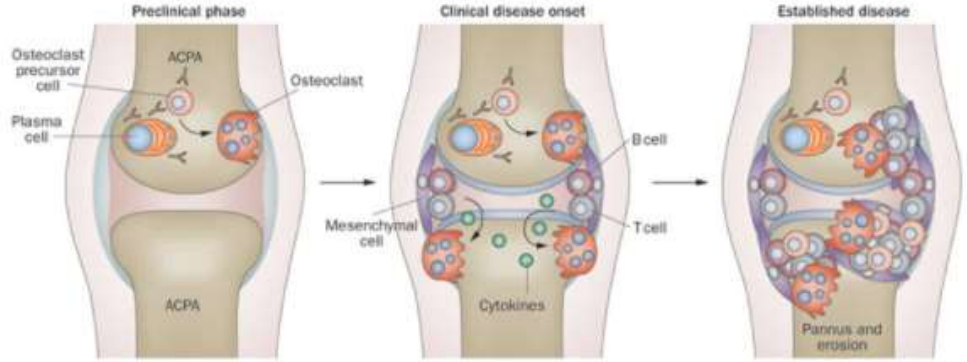
→ Soppressione dell'OC-genesi in vitro

Gabriel Herrero-Beaumont et al, Reumatol Clin. 2012

Wigerblad G, *et al. Ann Rheum Dis* 2016;**75**:730–738.

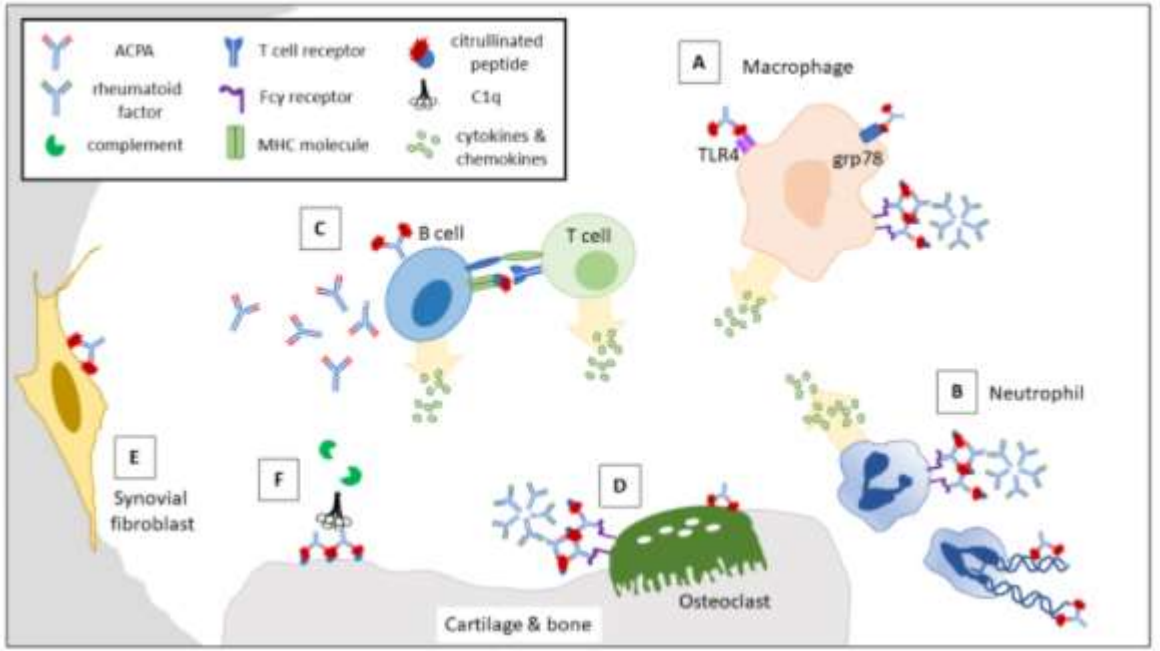
Autoantibodies to citrullinated proteins induce joint pain independent of inflammation via a chemokine-dependent mechanism



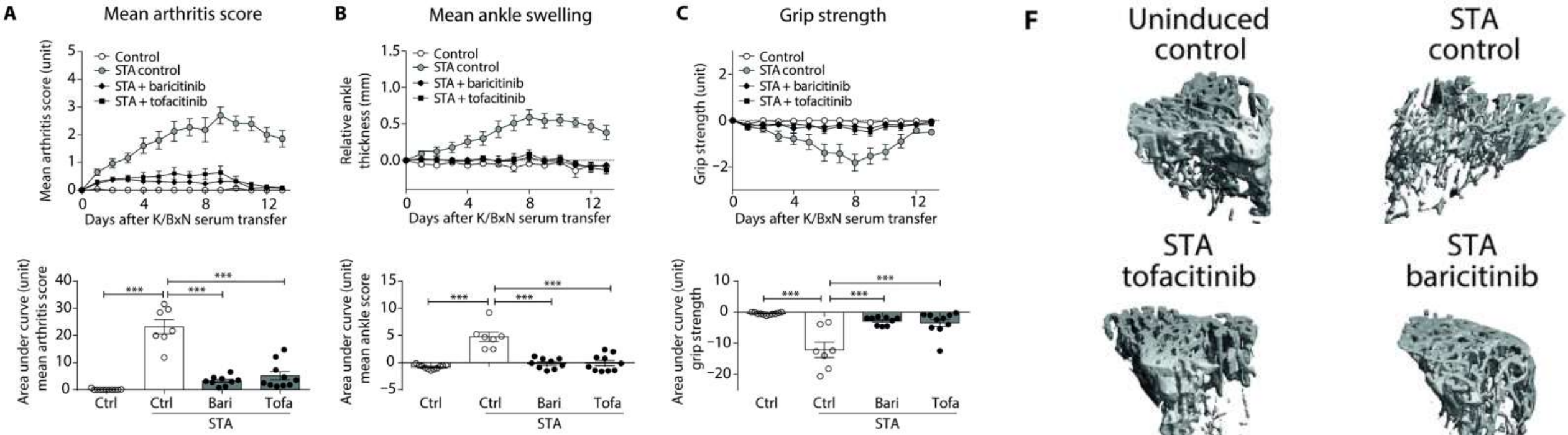


Chao-Yi Wu et al Int. J. Mol. Sci. **2020**, *21*(11), 4015;

Anti-Citrullinated Protein Antibodies in Patients with Rheumatoid Arthritis: Biological Effects and Mechanisms of Immunopathogenesis



- Perdita ossea mediata da autoanticorpi (ACPA) → ACPA → differenziazione degli osteoclasti
- Può precedere la flogosi
- L'ACPA e il fattore reumatoide (RF) hanno un effetto additivo sulla dimensione e sul numero delle erosioni.
- Effetti degli inibitori delle cellule T e B, come abatacept e rituximab, nell'AR



- **↓RANK-L/OPG nel siero.**
- **In vitro ↑ funzione OB (P <0,05) con sovraregolazione di osteocalcina e Wnt.**
- **Nessun effetto diretto sugli OC.**
- **AR JAKi effetti anabolizzanti ossei come evidenziato dalla riparazione delle erosioni ossee artritiche.**

Adam *et al.*, *Sci. Transl. Med.* **12**, eaay4447 (2020)

JAK inhibition increases bone mass in steady-state conditions and ameliorates pathological bone loss by stimulating osteoblast function

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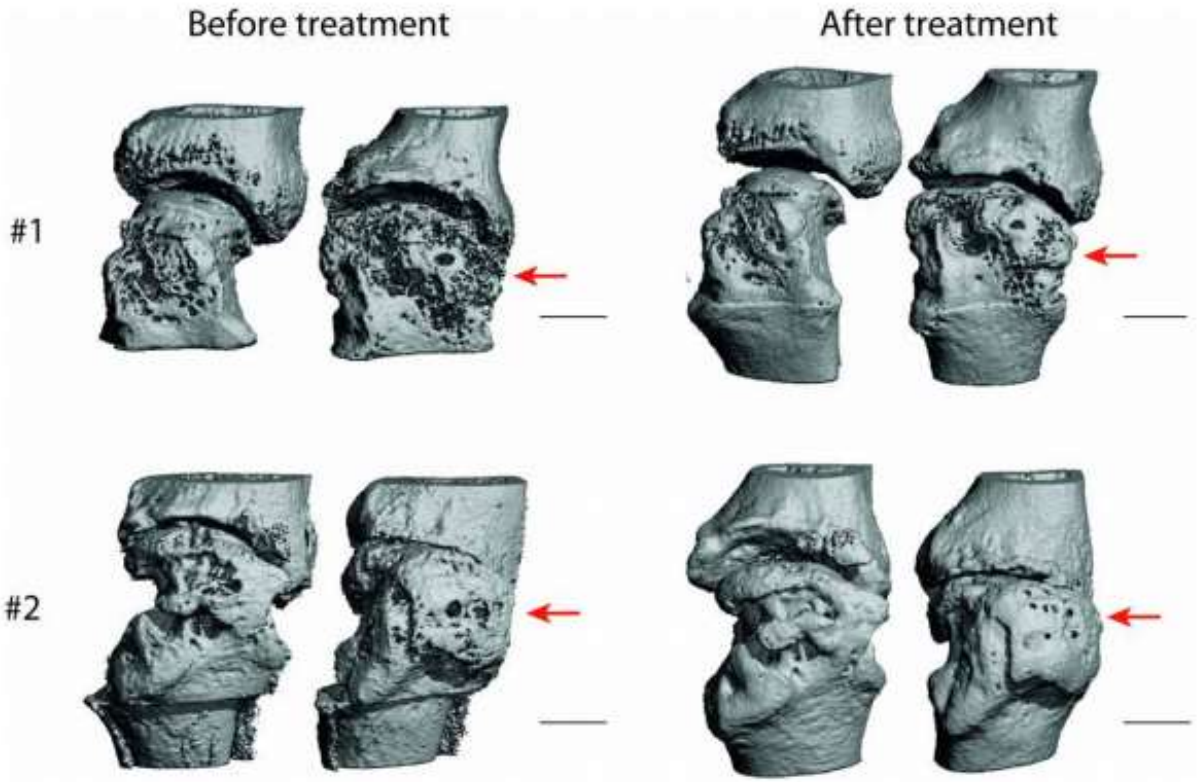
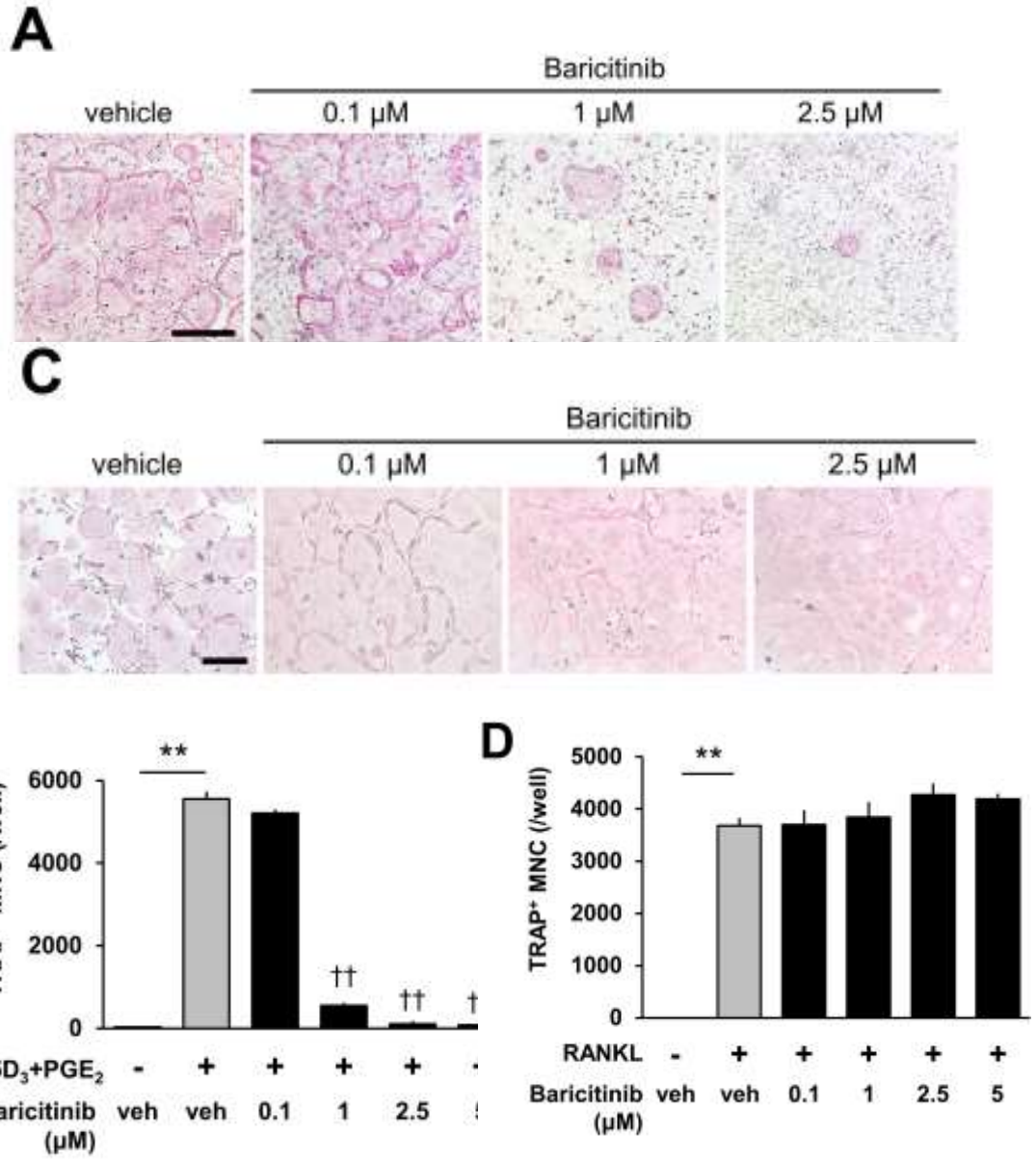


Fig. 7. JAKi by tofacitinib induces repair of bone erosions in patients with RA. 3D HR-pQCT images of metacarpophalangeal joints were generated before (left, each) and after treatment (right, each) from patients with RA ($n = 2$) who received 5 mg of tofacitinib twice daily for (top) 4 years and (bottom) 2 years. Scale bars, 5 mm. Arrows indicate exemplary regions of erosion where bone formation occurred.

A Jak1/2 inhibitor, baricitinib, inhibits osteoclastogenesis by suppressing RANKL expression in osteoblasts *in vitro*



Murakami K et al. PLoS ONE 12(7): e0181126 (2017)

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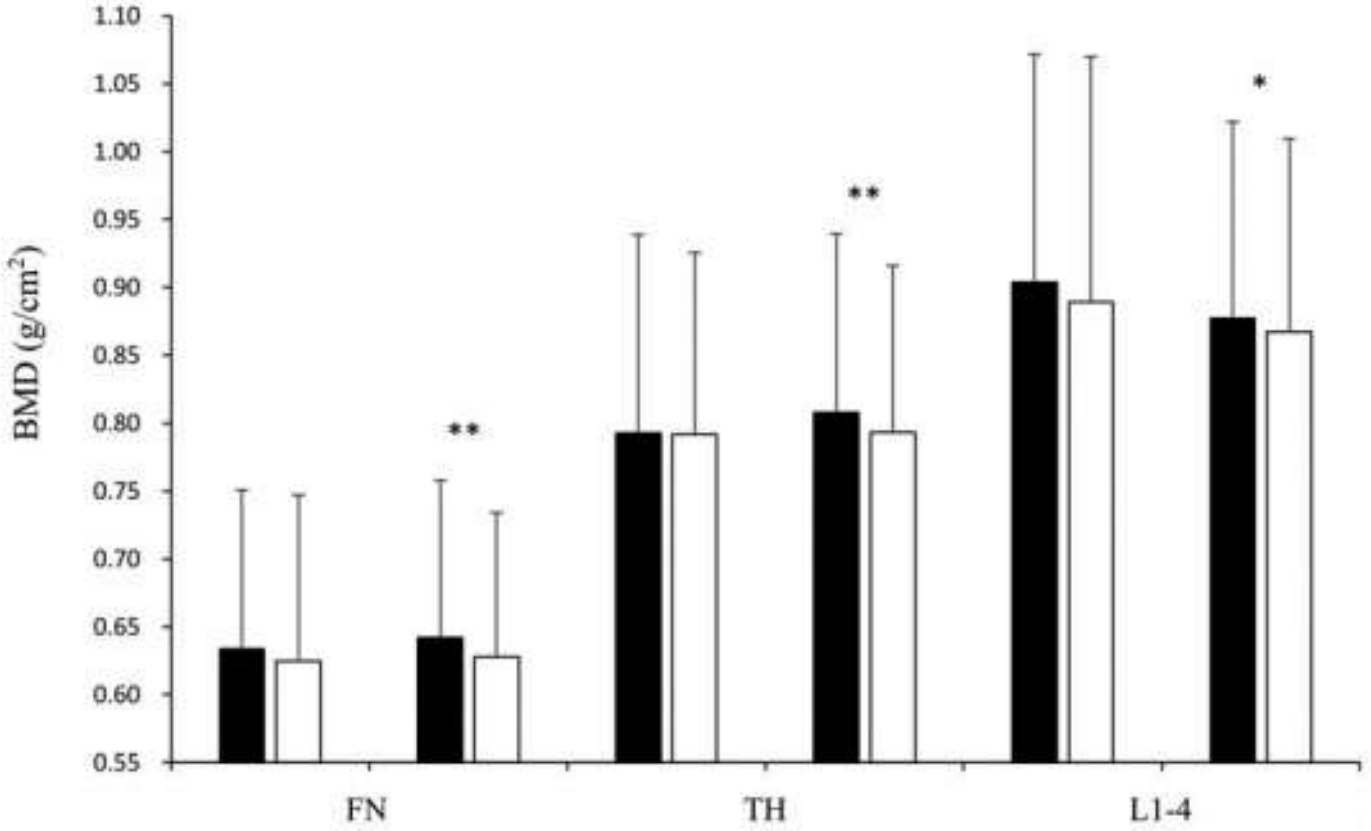
FIG. 2 Comparison of BMD at baseline and 3 years later at FN, TH and L1-4 in Group I and II participants



Group	I	II	I	II	I	II
■ baseline	0.634 ± 0.117	0.642 ± 0.116	0.793 ± 0.146	0.808 ± 0.132	0.904 ± 0.168	0.877 ± 0.145
□ 3 years later	0.625 ± 0.123	0.628 ± 0.106	0.792 ± 0.134	0.793 ± 0.123	0.889 ± 0.181	0.868 ± 0.142
p	0.15	<0.001	0.87	0.004	0.09	0.04

I, b/tsDMARDs + csDMARD; II, csDMARD; FN, femoral neck; TH, hip (total); L1-4, lumbar spine L1-L4.
** $p < 0.01$
* $p < 0.05$

- 92 pz b/tsDMARD group (Group I)
- 184 pz csDMARD group (Group II)
- anti-TNF 64.1%, TCZ 13.0%, ABA 12.0%, RTX 3.3%, class-switch 7.6% (2 pts TOFA)
- No cambiamenti significativi della BMD dpo 3 aa nel gruppo I
- Riduzione BMD nel gruppo 2

Jia-Feng Chen, Rheumatology 2020;59:2471–2480

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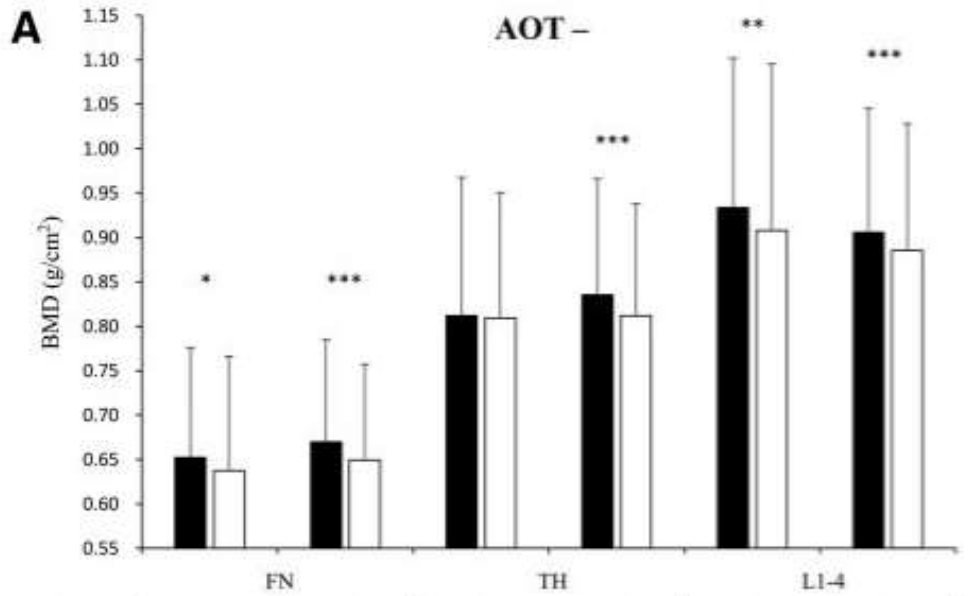
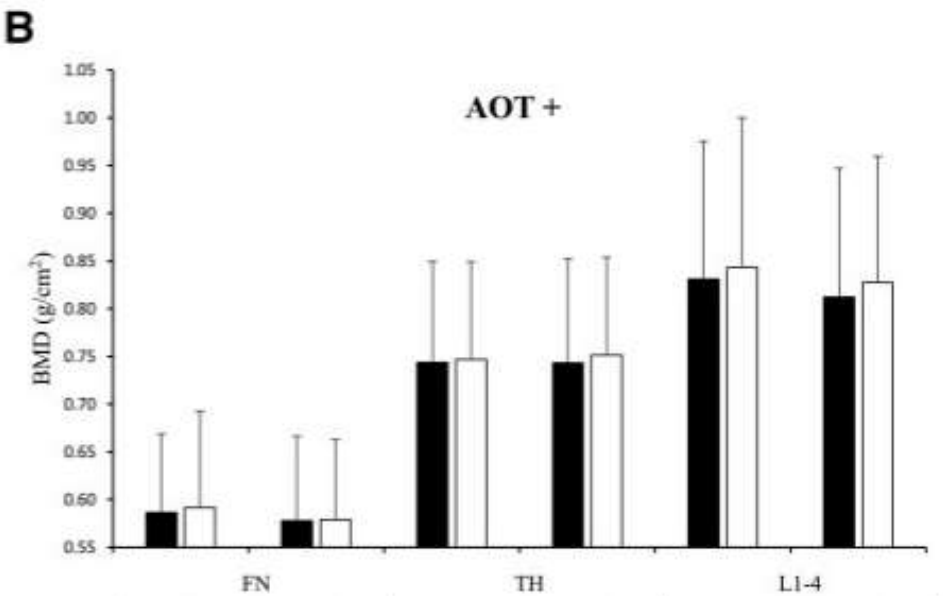
FIG. 3 Difference of BMD between baseline and 3 years later in patients receiving csDMARDs or adding on b/tsDMARDs, combined AOT use or not



Group	I	II	I	II	I	II
n	61	126	61	125	64	122
■ baseline	0.652 ± 0.124	0.670 ± 0.115	0.812 ± 0.156	0.836 ± 0.131	0.933 ± 0.168	0.906 ± 0.140
□ 3 years later	0.638 ± 0.129	0.650 ± 0.107	0.809 ± 0.141	0.812 ± 0.126	0.908 ± 0.188	0.886 ± 0.142
p	0.046	<0.001	0.75	<0.001	0.004	<0.001

AOT, anti-osteoporosis therapy, including bisphosphonate(s), denosumab, raloxifene, teriparatide
I, b/tsDMARDs + csDMARD; II, csDMARD; FN, femoral neck; TH, hip (total); L1–4, lumbar spine L1-L4.
***p <0.001, ** p < 0.01, * p < 0.05



Group	I	II	I	II	I	II
n	24	55	24	55	26	54
■ baseline	0.586 ± 0.082	0.578 ± 0.088	0.744 ± 0.106	0.743 ± 0.110	0.831 ± 0.144	0.812 ± 0.135
□ 3 years later	0.591 ± 0.101	0.579 ± 0.084	0.747 ± 0.103	0.751 ± 0.103	0.843 ± 0.157	0.827 ± 0.132
p	0.67	0.89	0.81	0.32	0.56	0.08

AOT: anti-osteoporosis therapy, including bisphosphonate(s), denosumab, raloxifene, teriparatide
I, b/tsDMARDs + csDMARD; II, csDMARD; FN, femoral neck; TH, total hip; L1-4, lumbar spine L1-L4.

Rispetto al basale, la BMD dei non utilizzatori di AOT nel Gruppo I è rimasta stabile in TH, ma è diminuita sostanzialmente a FN e L1-4 (P ¼ 0,046, P ¼ 0,004, rispettivamente). Tuttavia, i non utilizzatori di AOT nel gruppo II hanno dimostrato una significativa riduzione della BMD a FN, TH e L1-4 (tutti P <0,001) (Fig. 3A). La BMD in tre siti misurati è rimasta stabile o leggermente aumentata nei partecipanti che hanno ricevuto AOT in entrambi i gruppi, indipendentemente dall'uso di b / tsDMARD.

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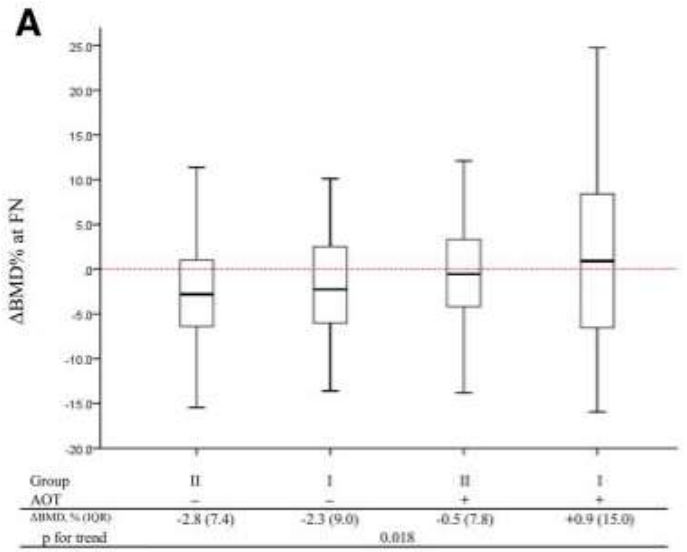
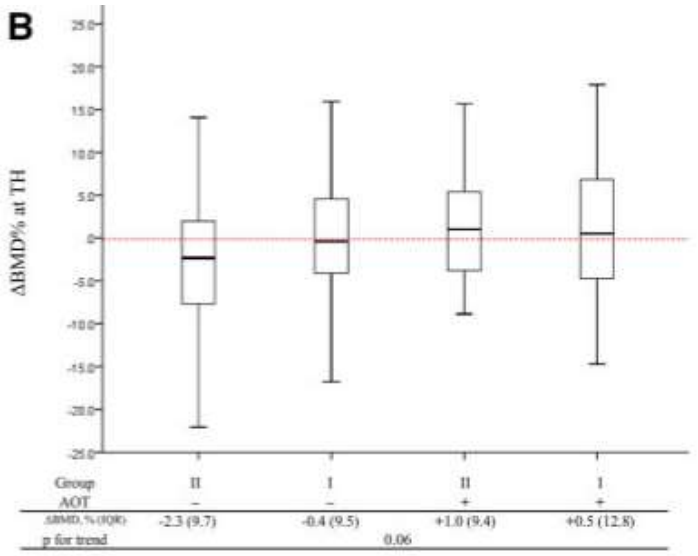
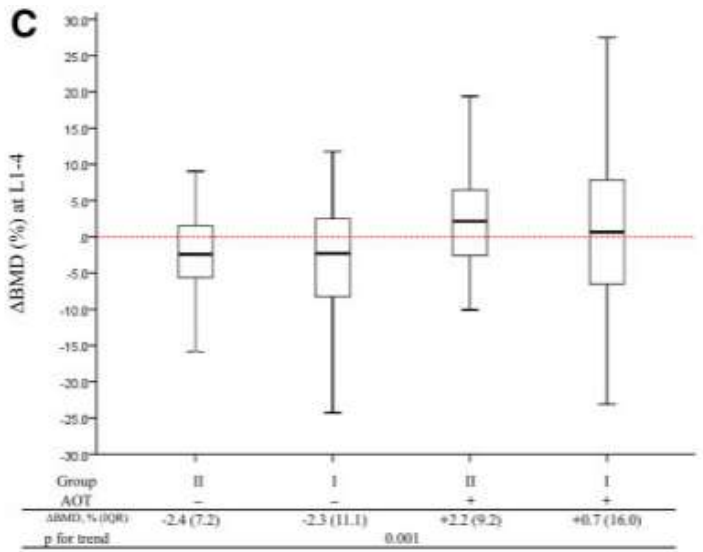


Δ BMD, % (IQR), percent change of BMD (second BMD-baseline BMD/baseline BMD in percentage), median% (interquartile range), I, b/tsDMARDs + csDMARD; II, csDMARD .
AOT, anti-osteoporosis therapy, FN, femoral neck



Δ BMD, % (IQR), percent change of BMD (second BMD-baseline BMD/baseline BMD in percentage), median% (interquartile range); I, b/tsDMARDs + csDMARD; II, csDMARD .
AOT, anti-osteoporosis therapy, TH, hip (total)



Δ BMD, % (IQR), percent change of BMD (second BMD-baseline BMD/baseline BMD in percentage), median% (interquartile range); Group I, b/tsDMARDs + csDMARD; Group II, csDMARD .
AOT, anti-osteoporosis therapy; L1-4, lumbar spine L1-4.

BMD change from baseline at different measured sites in group I and II, with or without use of AOT.

- La terapia a lungo termine b/tsDMARD aveva un effetto protettivo sulla perdita ossea in tutti i siti misurati.
- I pazienti in terapia convenzionale hanno sperimentato una sostanziale perdita in termini di BMD.
- I pazienti con AR che hanno ricevuto AOT hanno ottenuto un effetto protettivo sulla perdita ossea, indipendentemente da b/terapia tsDMARD o csDMARD.

Jia-Feng Chen, Rheumatology 2020;59:2471–2480

CONCLUSIONI

- AR malattia sistemica con alterazione di numerose attività metaboliche
- L'impatto dei diversi farmaci bDMARDs o tsDMARD sui vari metabolismi dipende dal ruolo delle citokine target in essi coinvolte
- L'effetto della terapia antireumatica avanzata è globalmente positivo sul dismetabolismo a vari livelli, espressione di regolazione e modulazione sulle alterazioni patologiche AR indotta